

The background of the cover is a microscopic image of cells, showing large, irregular white spaces (nuclei) against a blue, textured background (cytoplasm). Overlaid on this are several thin, dark lines and a prominent, dense, branching red structure that resembles a network or a cluster of cells, possibly representing a tumor or a specific cellular pathway.

Nano-Oncology, the Turning Point

Discover the Wave of Knowledge that Makes
Fighting Cancer with Nanotechnology Real

Texts and News Compilation by **Pr. Víctor Puentes** and **Josep Saldaña**.
Foreword by **Dr. Simó Schwartz**. Design by **Joan Escofet**.

Nano-Oncology, the Turning Point

Discover the Wave of Knowledge that Makes
Fighting Cancer with Nanotechnology Real

Berliner has come to the rescue in the most admirable way: He saw that the existing popular periodicals were sufficient to instruct and stimulate the layman; but he also saw that a first-class, well-edited organ was needed for the guidance of the scientific worker who desired to be put sufficiently au courant of developments in scientific problems, methods, and results to be able to form a judgment of his own.

Albert Eistein

In Honour of Arnold Berliner's Seventieth Birthday

(Arnold Berliner is the editor of the periodical *Die Naturwissenschaften*.)

The Wave

The fascination for the emergence of solid state properties, from the periodic table of elements to the extensive world of materials, and the behaviour of macromolecules immersed in a thermal bath where Brownian motion distributes entropy, is an old story that has been captivated the minds of scientist since, let's say, Democritus. This excitement is like a wave that is advancing, like a train of waves more precisely, reaching different sectors of science and society as time goes by. Thus, as Andre Nel with superparamagnetism or Richard Feynman with the small robotic hands that are able to make another set of smaller robotic hands endlessly until single atom manipulation seeded the last decades nanotechnology drive force. The wave of excitement that started in the physics departments in the XX century has been spreading among disciplines as chemistry, biology, engineering, medicine and pharmacology. Today there are nanotechnology centers and spin-off blossoming around campus all around the world and, significantly, important pharmaceutical companies, not prone to too much innovation, are introducing nanomaterials in their catalogues, as Abraxane acquired by CellGen. Up to now, the wave has been that of excitement and interest, rather than really delivering new paradigms to society (advanced nanomedicines, flexible displays, clean energy...). Thus, while new materials are being developed, this wave is serving to shake and push forward many technologies, as in the case of medicine, where if even no new nanoproducts make it to the market, the use of nanoparticles in medical research may breakthrough current clinical diagnosis and therapy. Finally, I would like to stress that the barriers today to clinical implementation of nanotechnology still are: difficulty of regulation, since protocols and agencies are not adapted to nano, lack of experience in industrial production of nanostructures and their conjugates and the fascinating versatility of matter at the nanoscale what is complicating controlled work and reproducibility.

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Nano-Oncology, the Turning Point

Discover the Wave of Knowledge that Makes Fighting Cancer with Nanotechnology Real

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Foreword

If nanotechnology refers to the design, production and application of structured materials, devices and systems at the nanometric scale, nanomedicine refers to their uses in diagnostics and treatments in the medical practice.

Far from the public perception that nanotechnology and nanomedicine are still trending topics of science fiction, a new emerging reality is deepening its roots in our society and people begins to realize that a new giant wave is going to smash our shores in the form of a technological revolution... and the impact might even go beyond imagination.

As expectations for a brighter future increasingly rise, new nanotechnology based systems improving our health and life expectancy are impatiently requested. As a consequence of this, a growing need to ensure that nanotechnology is developed at the right pace and within a controlled environment is becoming more and more evident because impatience often leads to frustration and social fatigue, which in turn hamper success. To this end, the correct identification of target stakeholders and end-users is fundamental. These include scientists, medical doctors and practitioners, general public and patient associations, regulators and policy makers, and financial, industrial and technological sectors among the most relevant ones.

In the first world, the progressive aging of the population due to the increase of life expectancy and a reduction in the number of births, the higher complexity of diseases and therapies, the saturation of the public health systems together with an increasing demand of welfare and the request for more cost-effective, fast and reliable personalized medicines, are urgently requiring better diagnostic and therapeutic solutions. No wonder, one of the stronger impacts of nanotechnology and nanomedicine is in drug development.

The potential wide range of applications of nanomedicine is generating a growing interest from both, research scientists and pharma industry. In fact, the number of scientific articles and related patents have experienced a very fast growing in the last 5 years, in particular in the drug delivery field that currently represents over 60% of the marketed products. This is because drug delivery systems can benefit in vivo from passive and active accumulation in target tissues, mediated by enhanced vascular permeability. The so called enhanced permeability

retention effect, which characterizes the altered neovessels found in tumors and inflammatory sites, and allows to increase the therapeutic window of current drugs either by decreasing their overall toxicity or increasing their efficacy, or both. This, together with the fact that nanomedicine conjugates enter the cell and in most cases deliver their cargo at the lysosomal compartment, makes nanomedicines very relevant in some medical areas such as oncology and lysosomal storage diseases, which are rare diseases with defective lysosomal enzymes.

These are two clear examples of the potential impact that nanomedicine can have at societal level, because society is highly sensitive to cancer and rare diseases. In the case of cancer because the tremendous impact of its high incidence and mortality, and in the case of rare diseases because these patients are often orphan of curative treatments. Patient associations are widely spread and very active in both cases. Because of this, the social perception is that nanomedicine can facilitate new effective cures and satisfy the social demand of solutions, which rises expectations and hopes, reinforced in turn by social media and newspapers. Thus, science, media and politics must be very careful to ensure the proper implementation of nanomedicine and avoid to rise false expectations because society easily turns hopes into frustration, dislike and despair, questioning credibility and humpering market interests and therefore, private and public investments. This is of crucial relevance because even if the market of nanomedicinal products is expected to be at the range of billions of dollars per year, the actual cost of bringing a nanomedicine to the clinical practice is humongous and therefore, a high amount of investment is required. Among other things, because scale up production of nanomedicines has to be feasible and capable to fulfill market demands.

At this moment, unfortunately, there are still some bottlenecks to be solved such as the industrial production under Good Manufacturing Practices (GMP) or specific legal and regulatory issues that should ensure adequate IP protection and safety. In the latter case, regulatory agencies such as EMA and the FDA are intensively working to provide content as regulators because nanomedicines do not behave as classical drugs and safety needs to be ensured before clinical approval. Specific protocols and assays to provide adequate physico-chemical characterization of nanoconjugates and their mechanism of action, scale up processes, efficacy testing procedures in in vivo relevant models and regulatory preclinical toxicity tests have to be properly addressed. Several guidelines have been released by these agencies in the last 10 years to provide an adequate regulatory framework, even though experience with marketed nanomedicines is still scarce. We will surely see amendments and improvements in the next few years to better fine-tune the current regulatory frameworks.

In the meantime, academy and drug developers are joining forces and setting up new multidisciplinary teams to come up with new drug delivery systems

and drug designs to face unsolved chemical and biological challenges. Indeed, multidisciplinary has joined the game and has become one of the strengths of nanomedicine research teams worldwide. Mixed teams of chemists, material scientists, biologists, physics, pharmacologists and biomedical doctors among other disciplines are now working together to face common challenges and sharing knowledge and infrastructures to achieve success. A new generation of multidisciplinary trained young scientists is taking a central play role on the field. And these scientists, are highly sought. Because all this is rarely found in most pharma companies worldwide, drug developers are relying their R&D into academic groups and specialized small and medium enterprises. This is contributing to a wider financial spread of resources and know how which favours employment and scientific progress in a more globalized manner.

However, on the other side of the coin, social awareness of potential negative impacts of nanotechnology affecting our environment and labor welfare are also on stake, and these need to be carefully and properly addressed. The presence of nanoparticles on the environment is unavoidable and it has been like this since the creation of our planet. Even though life on earth is fully adapted to this, the problem comes when these nanoparticles are toxic and their presence on the breathable atmosphere exceeds certain concentrations. This might happen during a volcano eruption but also when certain materials are used at industrial level. In fact, we know from historical experience that in the past the industrial use of some materials such as plumb or asbestos have caused poisoning and occupational lung disease. Preventing negative consequences like these is crucial to ensure the development of nanomedicine at industrial level and in particular, to define guidelines and rules on how to produce nanoparticles at a large scale without harming nature and people. As these are being considered, new nanodrugs are being developed and we will see a considerable number of them reaching the market and the clinical practice. The next few years will be crucial to see if nanomedicine fulfills the high expectations that it raises and if so, a new plethora of more effective medicines will be available in our society to ensure better welfare and healthy aging.

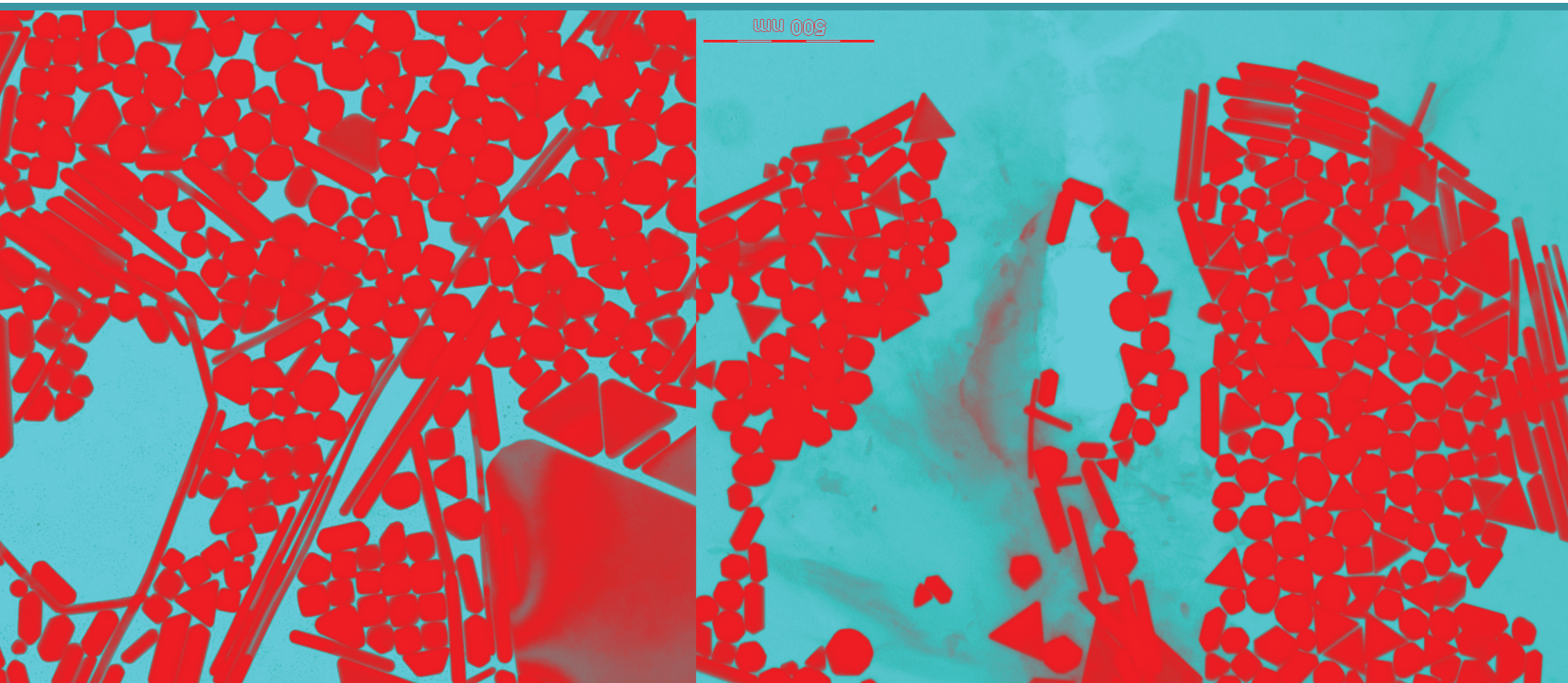
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Nano-Oncology, the Turning Point

PART I To Fight Cancer

Cancer is a leading cause of disease-related mortality, and with the increasing lifespan, it is predicted to be the cause of 50% of deaths in the 1st world population. Despite huge efforts, medical science has been unable to generate a “magic anticancer drug”, that is, a drug that can cure cancer completely and efficiently. The reason for this is that fundamental problems lie not in the drug itself, but in the way in which it is delivered and how it reaches the tumour. This lack of control and precision is present in other therapies, where a lack of specificity can thus damage healthy cells. One of the major goals in nanomedicine is to apply nanotechnology for the sustained, controlled and targeted delivery of therapeutic agents and radiosensitisers.



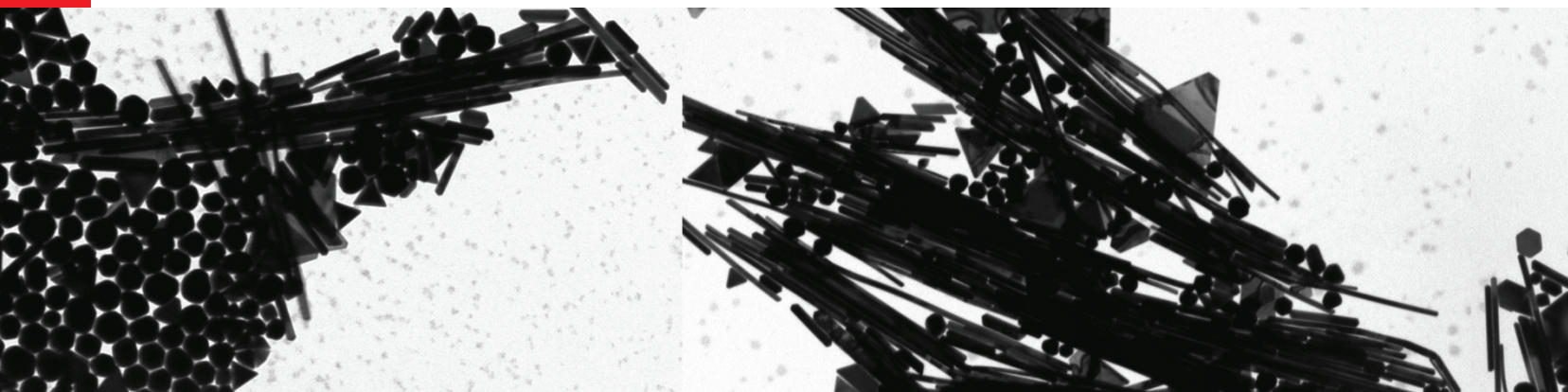
INTRODUCTION

Nanotechnology to Fight Cancer.

The last decade has seen a flourish in the study of the properties of nanoparticles (NPs) for medical applications. NPs display properties that are strongly determined by both morphology and the physicochemical context where they are immersed, allowing the monitoring and manipulation of biological states. In this context, inorganic NPs (iNPs) behave as “artificial atoms” since their high density of electronic states - which controls many physical properties - can be extensively and easily tuned by adjusting composition, size, shape and surface state, and used in biological environments. Organic nanoparticles and their hybrids mimic biomolecular structures themselves. Therefore, nanotechnology’s ability to shape matter at the scale of molecules is opening the door to a new generation of diagnostics, imaging agents and drugs for detecting and treating disease in its earliest stages. Perhaps more important, however, is the possibility to combine a series of advances which enables the creation of multimodal/multifunctional nanosized particles that may, for

example, contain drugs designed to kill tumours together with targeting compounds designed to home-in on malignancies and imaging agents designed to light-up even the earliest stage of cancer.

In fact, a description of cancer in molecular terms seems increasingly likely to improve the ways in which human cancers are detected, classified, monitored, and (especially) treated; for that, NPs, which are small and can therefore interact with molecular structures in a unique manner, may be especially suited to those tasks. For example, NPs are perfect candidates to be used in anticancer therapy, since they have shown passive accumulation in tumours due to the Enhanced Permeability and Retention effect (EPR).



The Enhanced Permeability and Retention (EPR) effect

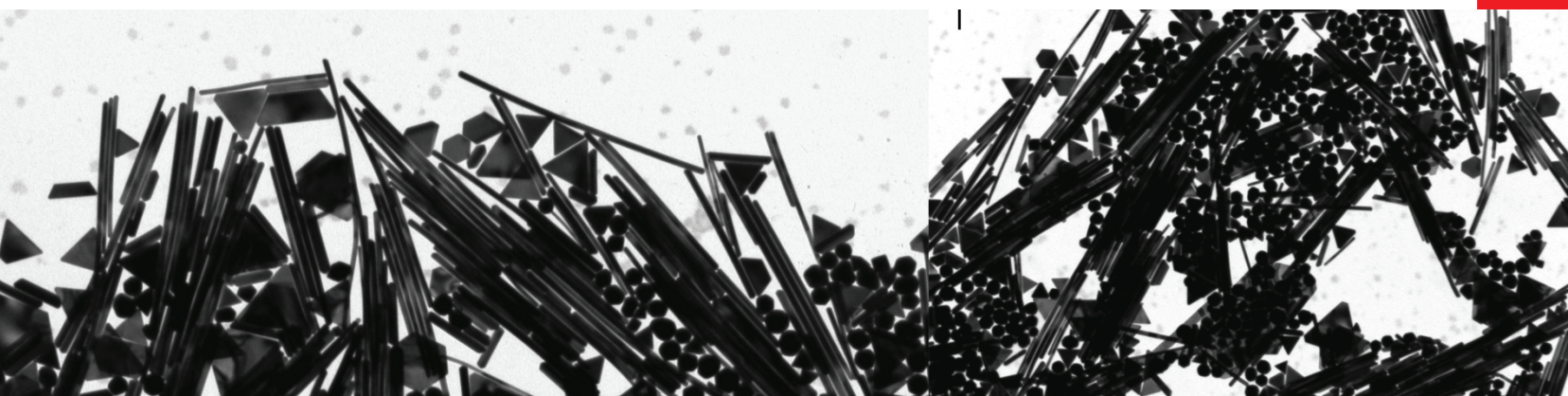
The Enhanced Permeability and Retention (EPR) effect is the property by which macromolecules (from tens to hundreds of nm) accumulate in tumour tissue much more readily than they do in normal tissues. The general explanation that is given for this phenomenon is that, in order for tumour cells to grow quickly, they must stimulate the production of blood vessels. Tumour cell aggregates as small as 150-200 μm start to become dependent on the blood supply carried by the neovasculature for their nutritional and oxygen supply. These newly formed tumour vessels are usually abnormal in form and architecture, with wide fenestrations, lacking a smooth muscle layer, or innervation with a wider lumen. Furthermore, for similar reasons, tumour tissues usually lack effective lymphatic drainage. Therefore, macromolecules (or NPs), which are unable to permeate through continuous vessels that irrigate normal tissues, permeate through tumour vessels. In addition, they are further retained into the tumour thanks to the lack of a functional lymphatic system.

Another example is the ability to encapsulate potent drugs in tiny particles measuring billionths of a metre, opening up new options for super-accurate drug delivery. Increasing precision hits at the site of disease with, hopefully, fewer side effects. Other potential applications include treatments for inflammatory disorders, heart and brain diseases, and pain. An interesting case is the use of the magnetic properties of iron oxide NPs as contrast

or hyperthermia agents or its iron content to treat anaemia, as in the case of feromuxitol®. In one case, NPs are injected intra-tumourally and stay there, and are regulated as a *device* or an implant. A nanomagnetic implant works as an antenna for tumour photoablation. On the other hand, aimed for systemic distribution, NPs have been regulated as *drugs*, indicating the broad range of action of nanotechnology in life sciences.

Promising hopes have been also raised on the use of nanobiosensors for the early detection of cancer biomarkers. Special plasmonic properties at the nanoscale enable the NPs to detect extremely low concentrations of analytes. Interestingly, as in the case of drug delivery devices, those tiny particles can be modified to obtain the functionality of interest, thus making them specific for the analyte of interest. The early detection of cancer is demonstrated to have a huge impact on the rate of survival after treatment.

Last, certain types of nanoparticles can be easily tracked by different means; for example, iron oxide NPs by MRI and metallic NPs by ultrasound or mass spectrometry. This allows researchers (and medical doctors) to follow the treatment, optimise doses and anticipate potential adverse effects. This is not usual in classic drugs, which are normally small molecules without specific signatures.



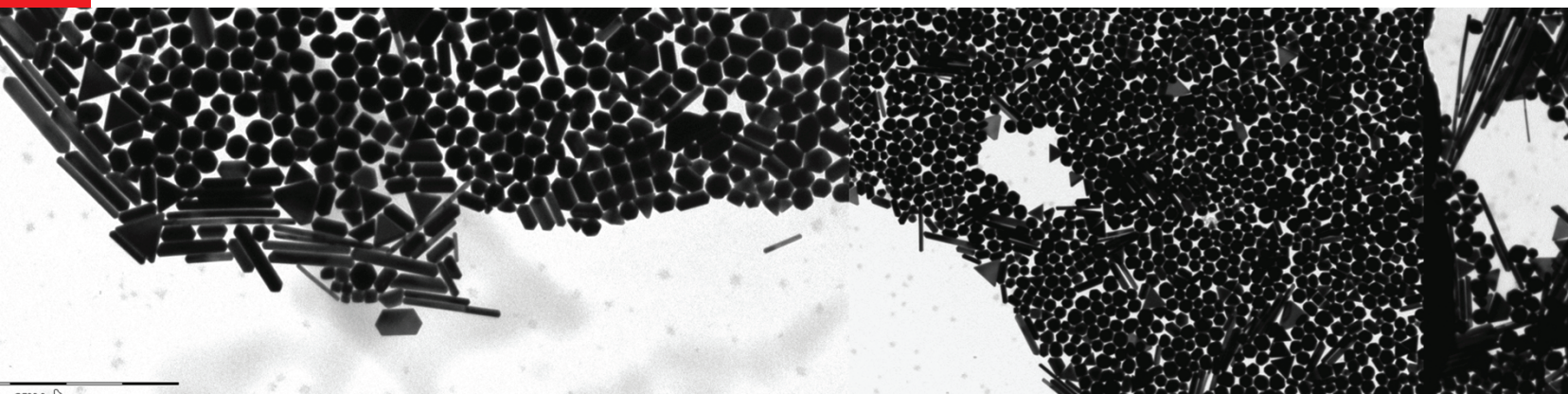
Cancer Nowadays.

The global death rate from cancer has declined only marginally over the past several decades, in contrast to dramatic reversals in death rates from heart disease, stroke, and infectious disease over the same time period [1]. In the past 30 years, the standard treatment has been surgery followed by radiotherapy and/or chemotherapy. If that fails, patients have less than a 10% chance of survival with other treatments.

There is an accepted general idea of a lack of breakthrough in the clinical treatment of cancer. An examination of the annual statistical data compiled by the American Cancer Society quickly reveals that the rate of mortality from cancer has changed very little over the past 60 years (except those consequences of reduced smoking rates and earlier diagnosis). Thus, despite progress in understanding cancer, its diagnosis and treatment have remained essentially unchanged for decades, and death rates from the disease are similar to those reported in 1950 [2]. In part, this is because

targeted cancer therapies, cancer biomarkers, and genomic medicine are still in the transition from basic research to clinical reality.

In addition, although cancer is often portrayed as a monolithic disease, it is anything but complex. There are more than 200 types of cancers, each with many variants and in every case, diagnosis, treatment and monitoring is somehow different. A report on the state of the art on cancer research can be found in the *Science* issue: *Frontiers in Cancer Research* [3]. Additionally, new drugs or active principles discovered from nature seem to have been exhausted, from the highest mountain fungi to the deepest ocean protozoa, and the new drugs designed are not yet working. It is in this context where nanotechnology emerges as a “disruptive technology”, with great potential to contribute to improved cancer treatment by the generation of new diagnostic and therapeutic products [4-7]. For instance, functionalised NPs can deliver



multiple therapeutic agents to tumour sites in order to simultaneously attack multiple points in the pathways involved in cancer.

“The future of oncology—and the opportunity to eliminate the suffering and death due to cancer—will hinge on our ability to confront cancer at its molecular level” was quoted not long ago by Andrew von Eschenbach, former director of the U.S. National Cancer Institute (NCI) in Bethesda, Maryland. Back in 2004, national funding agencies launched a multimillionaire cancer nanotechnology initiative [8] designed to foster interdisciplinary work among chemists, materials scientists, and biologists. In the last decade, Europe and Japan have also been investing heavily in nano-approaches to fight cancer, although nanotechnology funding agencies have not set up specific programs for cancer.



Normally, not all that is conceived becomes reality, however, what becomes reality, has been previously imagined. *The Magic Bullet* is a way to drive drugs towards the target while avoiding effects on the rest of the body. *The Fantastic Voyage*, scientist and a submarine are miniaturised to go and do medical work inside the body. Their fight against the immune system is epic. Both precluded developments on nanomedicine.

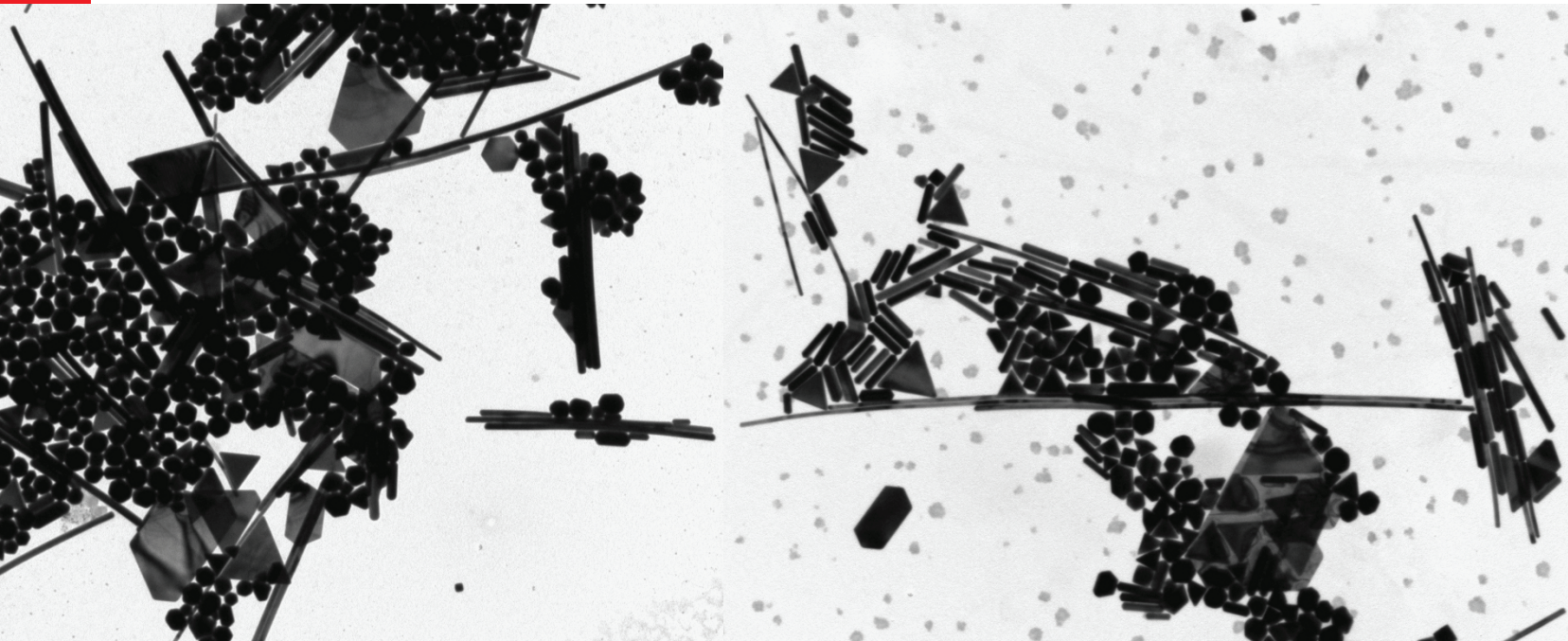


Nano-Oncology, the Turning Point.

When, almost 10 years ago, Science magazine dedicated a special issue on nanotechnology in cancer treatment [3], clinicians and pharmaceuticals did not consider it a real alternative yet. Currently, this perception may be changing thanks to the intense research efforts and exemplary bold initiatives to develop cancer nanotechnology [8, 9]. As a consequence, more than a dozen nanoparticle-based imaging agents and therapeutics are now either on the market, in clinical trials, or awaiting clinical trials [10] (or tabled in references [11]). Similarly, the use of superparamagnetic nanoparticles for photo-ablation (hyperthermia) of brain tumours has already been applied in the clinic [12]. Many indicators suggest that these days were the turning point for nanomedicine in oncology becoming a reality thanks to the fact that many believed in it years ago and have been working hard supporting its development: “Nanomedicine is playing a growing part in pharmaceutical research and development (R&D), primarily in the form of nanoparticle-based delivery systems for drugs

and imaging agents. Indeed, by some quantitative measures, the field is flourishing; over the past decade, there has been an explosive growth in the associated publications, patents, clinical trials and industry activity [13].”

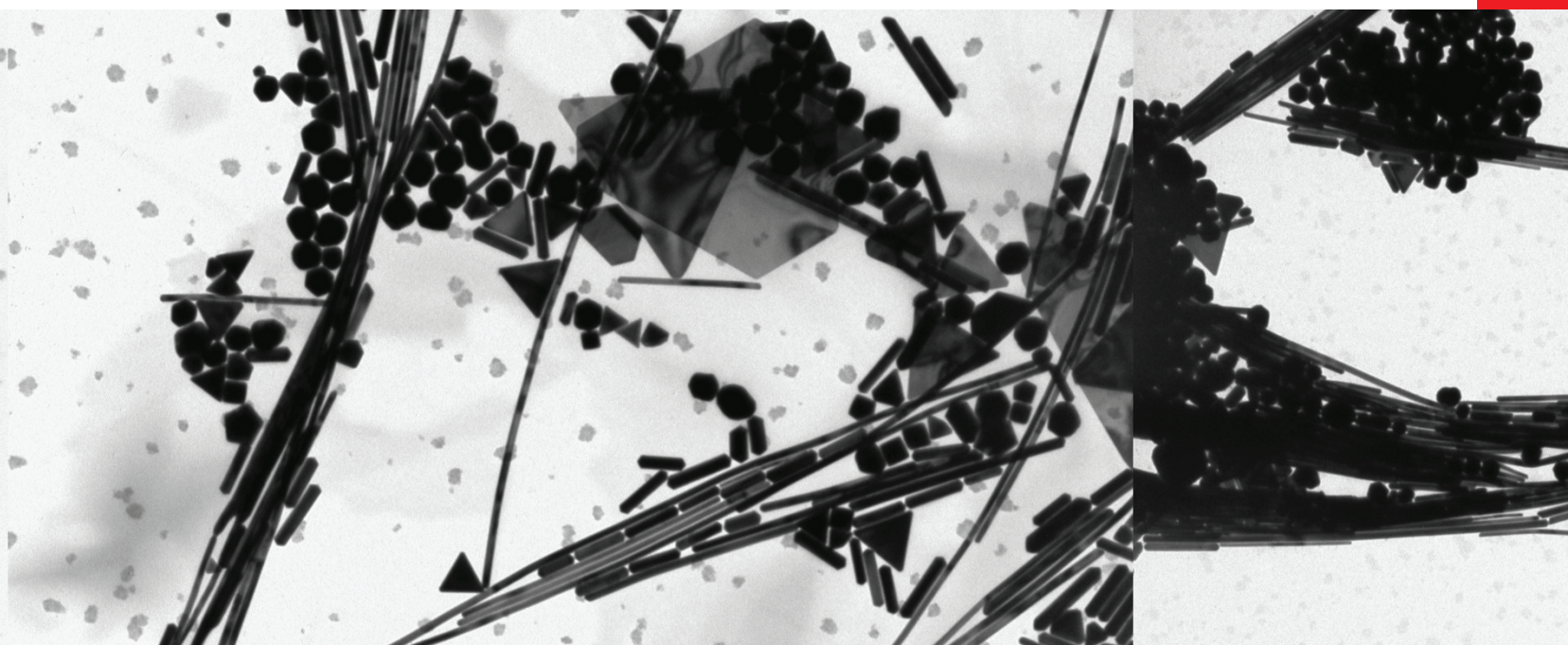
It is also important to note how recently pharmaceutical companies have been focusing efforts to bring nanotechnology solutions to the cancer treatment market. Thus, BIND, with their engineered Poly(lactic-co-glycolic acid) NPs, recently signed three development agreements with AstraZeneca, and CytImmune (Gold NPs) did the same with Amgen, while CellGen acquired Abraxane (Albumin NPs) not long ago in a billion dollar deal. Similarly, Nanobiotix, using heavy atom hafnium oxide NPs as a radiotherapy contrast agent, received strong French governmental funding to develop their enhanced radiotherapy technology, while MagForce continues to apply iron oxide NPs for thermal therapy in brain glioblastomas. This is happening now as fundamental research is



being translated into pharmaceutical and clinical development: “There is a new level of confidence in this approach among the big pharmaceutical companies ... We will see more and more products in clinical testing over the next few years and I think that is very exciting.” “Anything you can do to improve targeting of tumours rather than normal tissue - whether that is through an armed antibody or nanoparticle approach - increases the chance of success,” was said by Susan Galbraith, who leads AstraZeneca’s oncology research, in 2013 [14]. The Nanotechnology Characterization Laboratory (NCL), in coordination with the US National Cancer Institute (NCI), sponsored companies which developed agreements with big pharmacological industries in 2013 worth over a billion dollars, highlighting a new interest in using such tiny carriers to deliver drug payloads to specific locations in the body. Among many other venture-backed nanomedicine firms are Selecta Biosciences, which has a deal on food allergy vaccines with Sanofi, and Liquidia Technologies, which is allied with GlaxoSmithKline

on vaccines and inhaled products. In general, companies are increasingly focused on better drug targeting to increase efficacy and lessen the collateral damage caused by medicinal “carpet bombing” - a particular problem in cancer, where toxic compounds are needed to kill tumours. Surprisingly, it seems that we have few other alternatives to bring new drugs to the clinic, or, in general, few ways to promote progress other than via pecuniary profit.

Recent scientific advances have changed the game. PLGA nanoparticles, for example, are programmed to reach the right spot using targeting molecules that recognise specific proteins linked to disease on the surface of cells. They also have a stealth covering that shields them from the immune system, in order to minimise adverse reactions. Other approaches use tiny particles of gold as drug carriers. The work on drug-carrying NPs parallels advances in using so-called “armed antibodies” to deliver drugs directly to cancer cells - an



approach that is also currently being developed. For example, Genentech (Roche) won U.S. approval in February 2013 for Kadcyla, its first such antibody-drug conjugate, which treats breast cancer with fewer side effects. “All these developments have prompted companies to look at new avenues because the older ways of using drugs haven’t worked so well” (Robert Langer).

Thus, the potential of clinical nano-oncology has been increasing steadily for the last decade, even if it can be considered a 60 year-old initiative, when gold NPs were tested as radioenhancers for cancer treatment. There is a general agreement that the world’s first nanomedicine was actually approved back in 1995, when U.S. regulators gave a green light to Doxil for the treatment of Kaposi’s sarcoma. Doxil, a hollow fatty ball known as a liposome with a cancer-killing drug inside it, was a breakthrough, yet few other nanomedicines have followed. However, before nanotechnology, liposomes were already being used in the clinic

and there are reports of the explorative use of gold nanoparticles as radiotherapy enhancers in the dawn of radiology in the 1950s. Now, it is readying to deliver its full diagnostic and therapeutic potential. The fields of action can be classified in diagnosis, imaging, drug delivery, hyperthermia and theranostics, simultaneous diagnosis and therapy and therapy monitoring. Personalised health care, rational drug design and targeted drug delivery are some of the proposed benefits of a nanomedicine-based approach to therapy. In fact, it has been acknowledged that one of the most promising societal impacts of nanotechnology is in the area of nanomedicine. Thus, nanomedicine is being put to work in diagnosis, with tiny particles used to improve imaging in scanners, as well as rapidly detecting some serious infections. In future, researchers hope to combine both treatment and diagnostics in a new approach dubbed “theranostics” that would allow doctors to monitor patients’ status via their medicines.



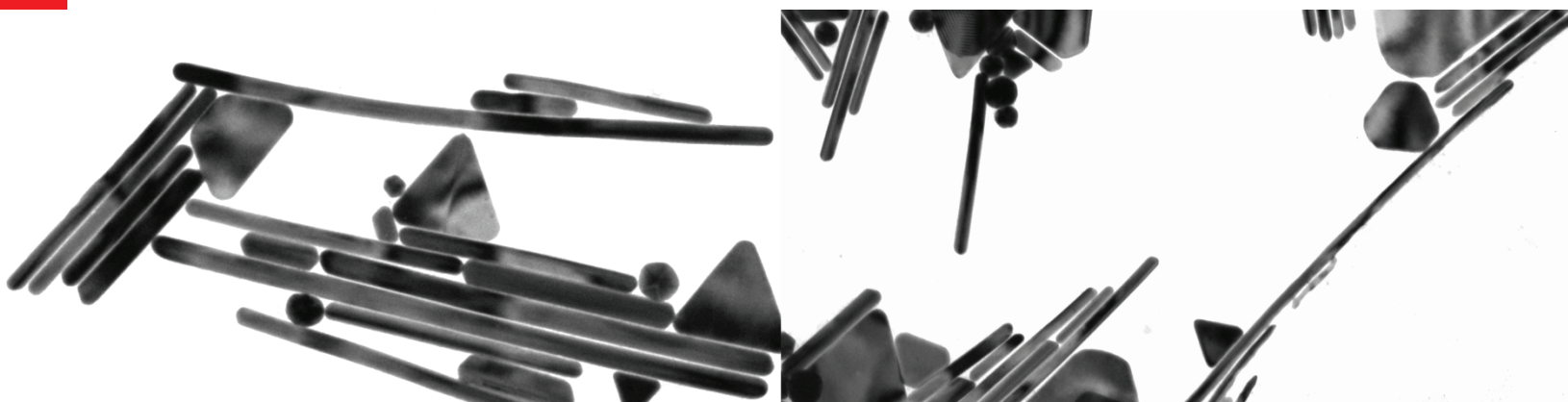
WHICH NANOPARTICLES?

Nanoparticles in Medicine.

A plethora of nanoparticles (NPs) including polymeric, liposomes, dendrimers, metallic, oxide, etc., have been used to design nanocarriers for drug delivery [4, 15]. Nanoparticles made of polymers, gold and even graphene - a newly-discovered form of carbon - are now in various stages of development. In cancer alone, 117 drugs are being assessed using nanoparticle formulations, although most have yet to be tried on patients, according to Thomson Reuters Pharma data.

The European Technology Platform on Nanomedicine, at its General Assembly in London in November 2012, identified 18 marketed pharmaceutical nanomedicine products, mainly against cancer, immunosuppression and bacterial, viral or fungal infections, chronic kidney disease or multiple sclerosis, mainly using PEGylated drugs and liposomes. Also, 44 marketed nano-delivery products were identified, with similar targets and materials, but including others as treatments of menopause, neonatal respiratory distress, macular

degeneration, and Alzheimer disease. There are also molecules prepared in a nanocrystal form, where this form is the vehicle, and from which the active component is released while the vehicle disintegrates. There are also more than 15 marketed imaging, diagnosis and biomaterial products based on magnetic iron oxide, as well as gold and hydroxyapatite for bone repair. Finally, more than 70 nanomedicinal products were reported to be in clinical trials in 2012, spanning many fields of medicine. To observe these data in more detail, please see reference [9]: As can be observed, despite the fact that cancer absorbs the majority of medical and nanomedical innovations, a field which is expected to grow is vaccination and adjuvancy, due to the inherent advantages of nanoparticles to address the immune system and the development of superbacteria that are resistant to antibiotics. In a recent essay, the director in chief of the NIHR [16], speculated about medicine in a world without antibiotics: no surgery, no implants, no chemotherapy, no radiotherapy, etc., where hygiene,



stimulation of the immune system and vaccination would become the standard tools to fight against infection.

TO KNOW MORE

ETPN General Assembly London 2012

Moving Nanomedicine towards H2020

<http://www.etp-nanomedicine.eu/public/news-events/events/events-archive/etp-nanomedicine-general-assembly-2012/presentations/121030%20Moving%20nanomedicine%20towards%20H2020%20London.pdf>

ETPN white paper H2020

NANOMEDICINE 2020

http://www.etp-nanomedicine.eu/public/press-documents/publications/etpn-publications/etpn-white-paper-H2020/at_download/file

ETPN report 2009

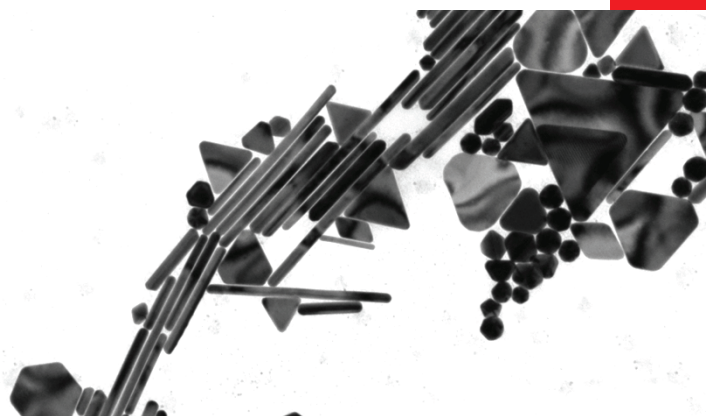
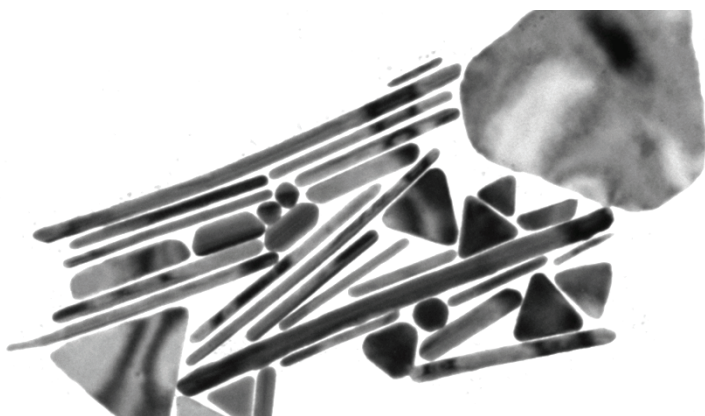
Roadmaps in NanoMedicine. Towards 2020

http://www.etp-nanomedicine.eu/public/press-documents/publications/etpn-publications/091022_ETPN_Report_2009.pdf/at_download/file

ETPN opinion paper 2010

The Impact of Open Innovation on (Nano-) Healthcare R&D in Europe

http://www.etp-nanomedicine.eu/public/press-documents/publications/etpn-publications/100526_ETPN_OpinionPaper_Eaton_Weltring.pdf/at_download/file

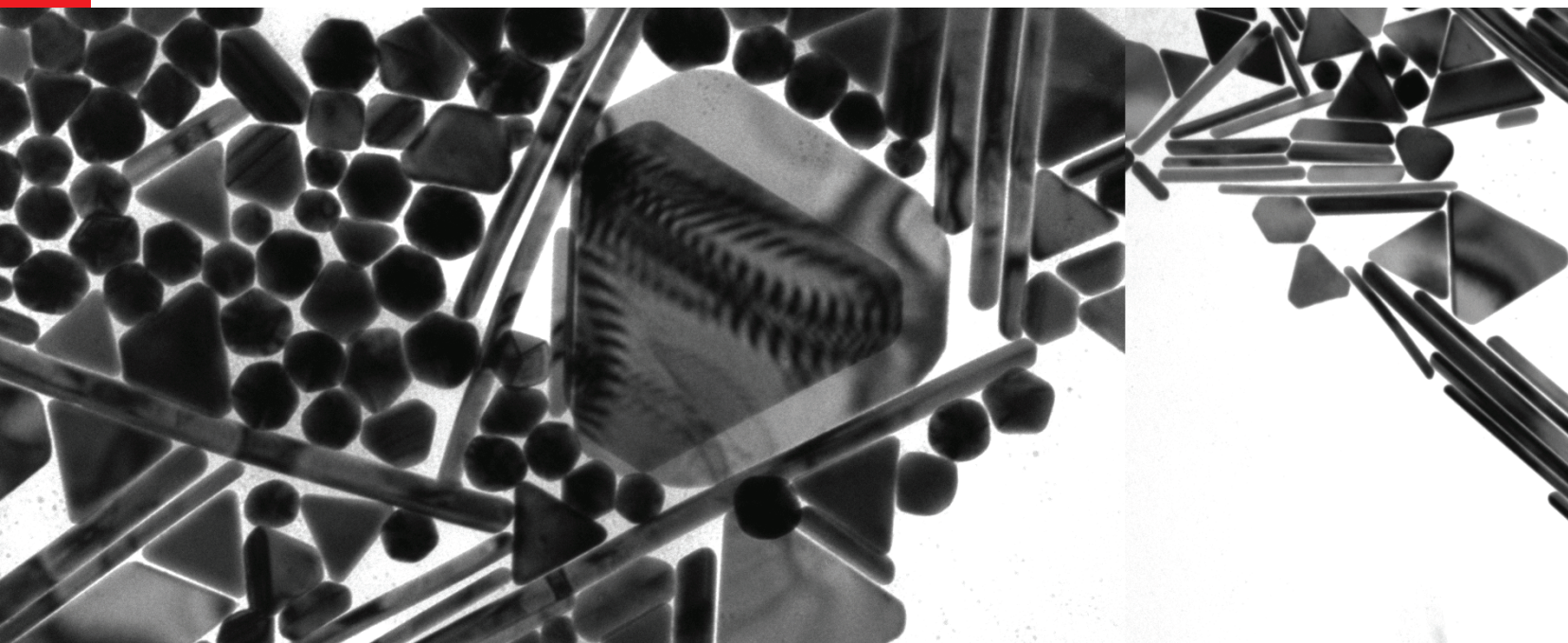


Nanoparticles for Drug Delivery. Characteristics and Advantages, All Together.

Some carriers display a series of natural advantages. Inorganic NPs can be produced in large quantities and narrow size distributions. Their small size, similar to those of proteins, allow long lifetimes in blood, and the better use of the enhanced permeation and retention effects observed in solid tumours, and tumour penetration. Controlled NP surface chemistry exists that can be optically monitored. Similarly, doxorubicin natural fluorescence is quenched by gold NPs. Therefore, its release can be optically observed. However, there is a much broader tradition of using organic NPs and they arrived in the clinic before inorganic NPs, as in the case of Doxil, which is a liposomal formulation (hundreds of nanometres in size, biocompatible and biodegradable) of doxorubicin that increases the solubility of the active ingredient and modifies the dosage by sustaining it over time [17]. However, although organic NPs are very simple to make and normally highly biodegradable, they are difficult to characterise and it is hard to monitor and trace their evolution and biodistribution inside the body.

The control over size is a key point in the use of NPs in biomedicine, since it influences important biological properties such as interactions with proteins, biodistribution and clearance rates. The variety of sizes of NPs that can be easily obtained has facilitated a better understanding of the role played by this property in parameters that are important for cancer treatment with NPs such as accumulation in tumours and tumour penetration. It is widely accepted that a compromise between accumulation and penetration has to be reached (i.e. larger NPs are more readily accumulated in the tumour, but they are restricted to regions on the periphery, close to blood capillaries, whilst smaller NPs are able to penetrate deeper into tumours).

Thus, it is clear that control is essential from the very beginning with regard to the development of nanovehicles. The size and shape of the different NPs are well controlled by the nanotechnologist community, which facilitates a better design of these novel drug delivery systems. For example, for stable, low interacting and non-immunogenic

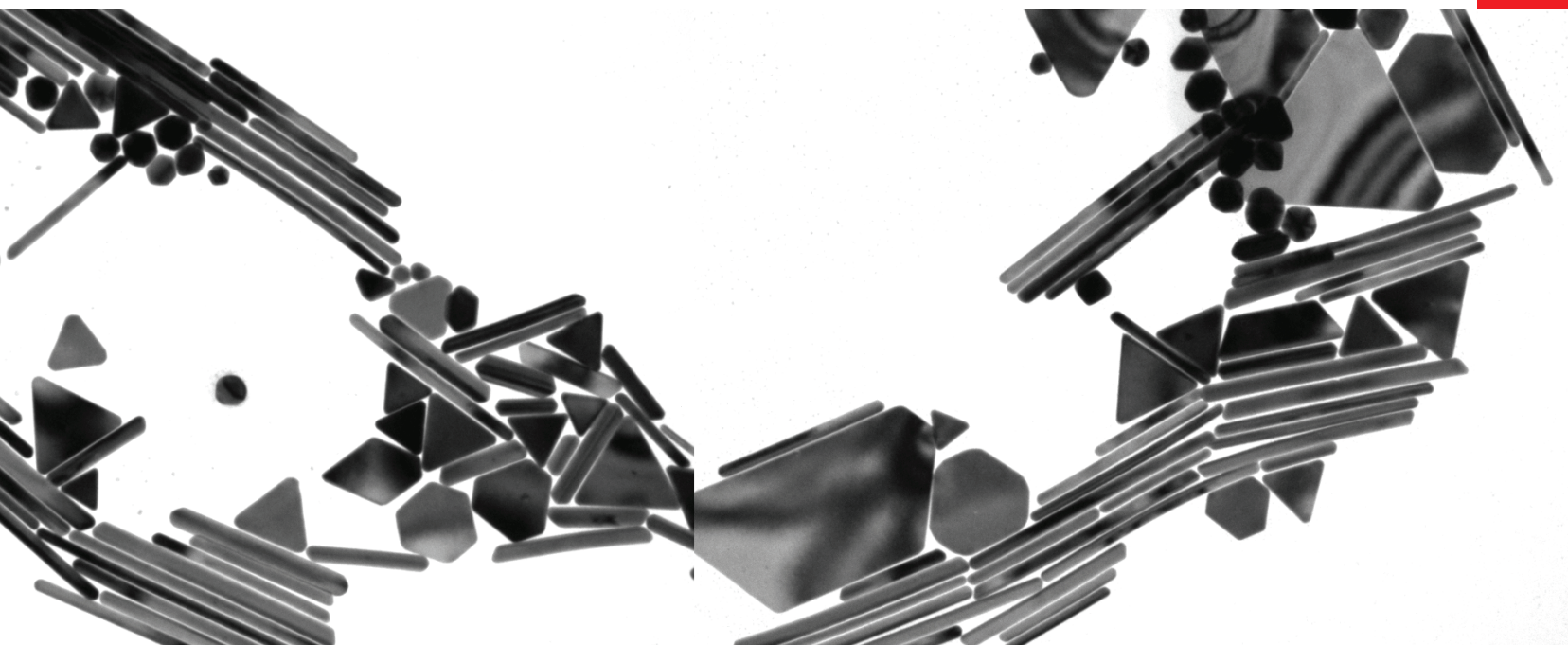


NPs, one could say that the final fate of the NPs will then be strongly influenced by their size, since the smallest NPs (<6 nm, core + surfactant) are rapidly cleared by the kidneys and the largest ones (>100 nm) are easily removed from the circulation by the immune system [18]. Intermediate sizes showed the best accumulation and penetration in tumours; in this range, other parameters such as the presence of stealth agents or different surface charges should be tuned on a case by case basis to achieve the desired behaviour.

Shape is also well controlled nowadays. Hence, exotic shapes such as nanorods, nanostars, nanocages and nanoshells, amongst others, can be synthesised in nanotechnology labs [19]. This not only demonstrates that the nanotechnology community is able to prepare almost any shape-material combination of interest, but has opened up a world of interesting properties to explore other fields such as biomedicine. Hence, special features related to these exotic NPs have been

studied recently. Although spherical NPs are usually the chosen option for use as carriers due to their simple synthesis and easy functionalization, other shapes such as nanorods or nanoboxes have also been used for biomedical applications. The different shapes often possess different properties. For example, the extravasation rate of rod-like nanoparticles was reported to be higher than that for equivalent spheres due to tumbling effects [20].

Some of these NPs have special physicochemical properties that make them appealing for use not only as vehicles but also as effectors themselves. For example, some AuNPs present a surface plasmon resonance (SPR) in the near infrared (NIR) region. The region of the spectra in which this SPR absorbs is strongly dependent on the shape of the NPs. Thus, NPs can be easily designed to absorb at specific desired wavelengths. This is commonly achieved by using anisotropic NPs (e.g. gold nanorods, and nanoplatelets). NIR is a region of the light spectrum where there is transparency (like



water in the visible range), simplifying, a window of transparency, the water window, between the overlapping light absorption of water, haemoglobin and melanin, basically. In photothermal therapy, NIR light is absorbed by NPs, delivering toxic amounts of heat just in the vicinity of the NPs, but not in unlabelled tissue [6]. At those wavelengths, photons can penetrate deep into tissue enabling the tumours to be reached. Magnetic fields are also highly penetrating; therefore, iron oxide NPs are used for hyperthermia when excited in the radio frequency regime. However, the spatial resolution for imaging or hyperthermia is above 3 orders of magnitude in the case of NIR.



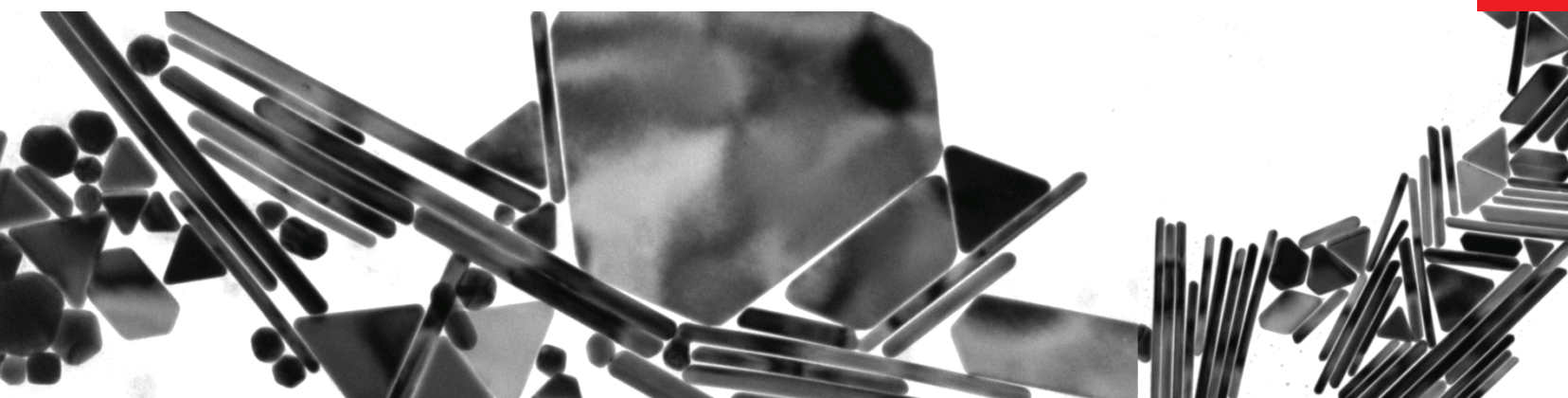
Multimodality.

Particularly appealing and suitable for nanotechnology is what can be called “treatment cocktails”, including synergetic effects of different chemotherapeutic agents, radio, immune and thermal therapy. Ahead of the lack of new drug discovery, combinatorial effects for improving current therapeutic strategies might be the key for fighting cancer or other diseases. In this respect, nanoparticles/nanostructures are now reaching a level of complexity which might allow the easy combination of different techniques that are already in use in clinics.

It seems clear in the state of the art that single-modality treatments are close to exhausted and limited; thus, they are not able to cure the cancer just by themselves. For example, surgery may disperse tumour cells and trigger faster metastatic processes, while radiotherapy and chemotherapy may be inefficient when tumour cells are not highly susceptible to them due to radio-insensitivity and the multidrug resistance of cancer cells. Also, it

is unlikely that a “magic anticancer drug” (that is, a drug that can cure cancer completely and efficiently) will be discovered in the next few years. The reason for this is that fundamental problems do not lie in the drug itself, but in the way in which it is delivered, how it travels through the body and how it reaches the tumour. This lack of control and precision is present in many other therapies, where a lack of specificity forces *treatment* in many areas of the body where it is not desired and damages healthy cells. Instead, multimodality treatments can do an excellent job, superior to any single treatment in current practice. This is simply because the combination of drugs and treatments are designed in such a way that primary effects add up while secondary do not.

One of the first observed synergetic effects among therapies that was initially not intended, consisted of the combined effect of chemo- and radiotherapy with cisplatin. Given together, the results were better than the benefits of the separate chemo- or



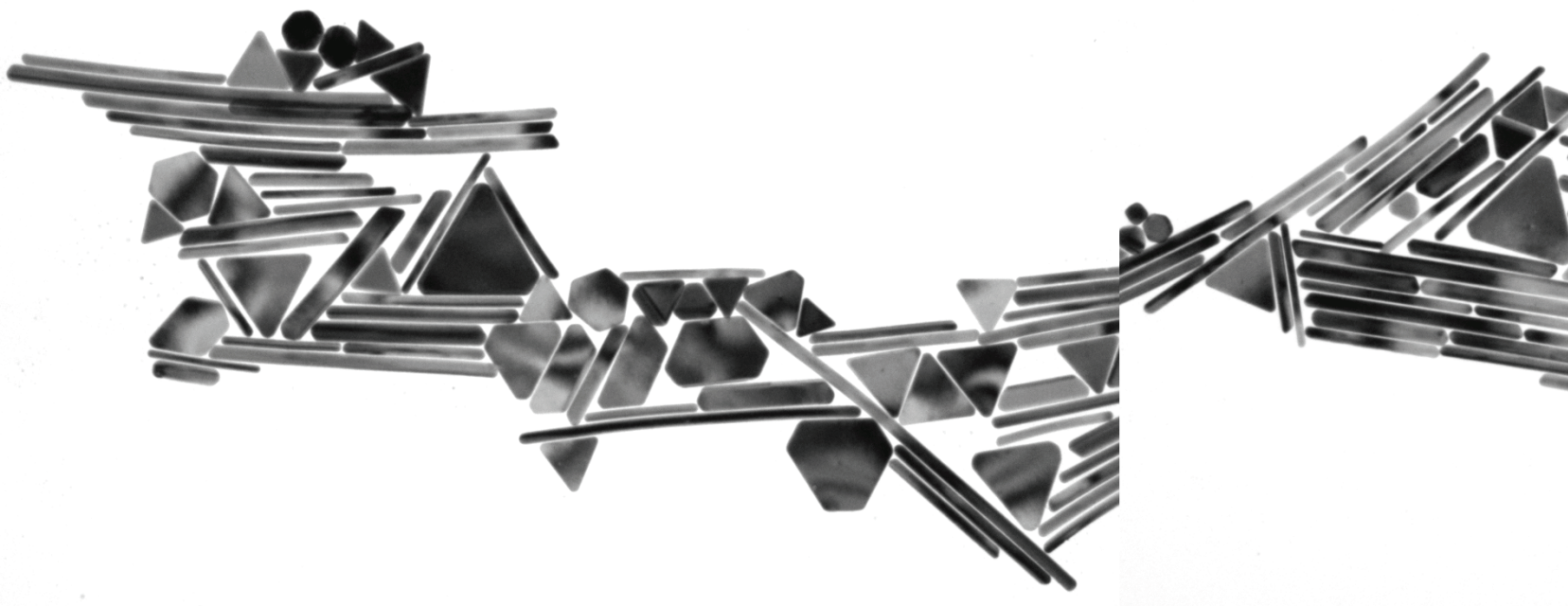
radiotherapy. This is because the Pt atom of the cisplatin molecule is very heavy and results naturally as a radioenhancer. The exact mechanism of action is still unknown, but it is more widely accepted that the role of Pt in radiosensitising is binding to the DNA, which disrupts the mechanisms of DNA repair from the damage produced by the high energy photons. The damage to the DNA after radiation is mainly produced by the radicals that are generated when H_2O is irradiated; these radicals break DNA strands. Fortunately, in healthy conditions, we have a very efficient DNA repair system (otherwise we would be mutating on a daily basis) that deals with these breaks in the DNA; however, it is much more difficult to deal with when something (cisPt) is attached to the DNA. Then, ultra-specialised proteins that recognise DNA lesions cannot function and the system collapses, sending the cell towards apoptosis.

Additionally, if cisplatin is attached to the DNA (as it does to perform its therapeutic antineoplastic effect), the radioenhancing effect is directed at the target with molecular precision (radiotherapy also tries to damage the DNA of dividing cells which is more susceptible during mitosis). Additionally, damaging an already damaged cell appears to be very effective in tumour treatment. These questions are also addressed by nanomedicine, where carefully engineered nanocarriers can play a

significant role. Therefore, medical advances must support and enhance multimodal approaches, and nanomedicine can provide a superior platform for such multimodality treatments.

An example is the use of AuNPs as carriers for the sustained, controlled and targeted delivery of therapeutic agents and radiosensitisers. For example, the NPs can easily transport poorly soluble drugs, such as doxorubicin, towards the liver where they are passively accumulated. Moreover, once the drug load is transported and released, the carrier serves as a radiotherapy enhancer and hyperthermia agent. Ultimately, the release of the drug can be triggered by the radiotherapy itself coupling both treatments at the molecular level. Such nanocapsules thus act as “nanobots”, which enable multimodality treatments, reaching a new level of precision and efficiency. This is important in the clinic, since the multimodal treatments of cancer consist of the application of a combination of doses of different chemical and physical therapies in such a way that, for example, determine the relative concentration of two drugs in the same particle, thus impeding further modulation of the doses individually as the clinician will require (then requiring a cocktail of nanocarrier substances).

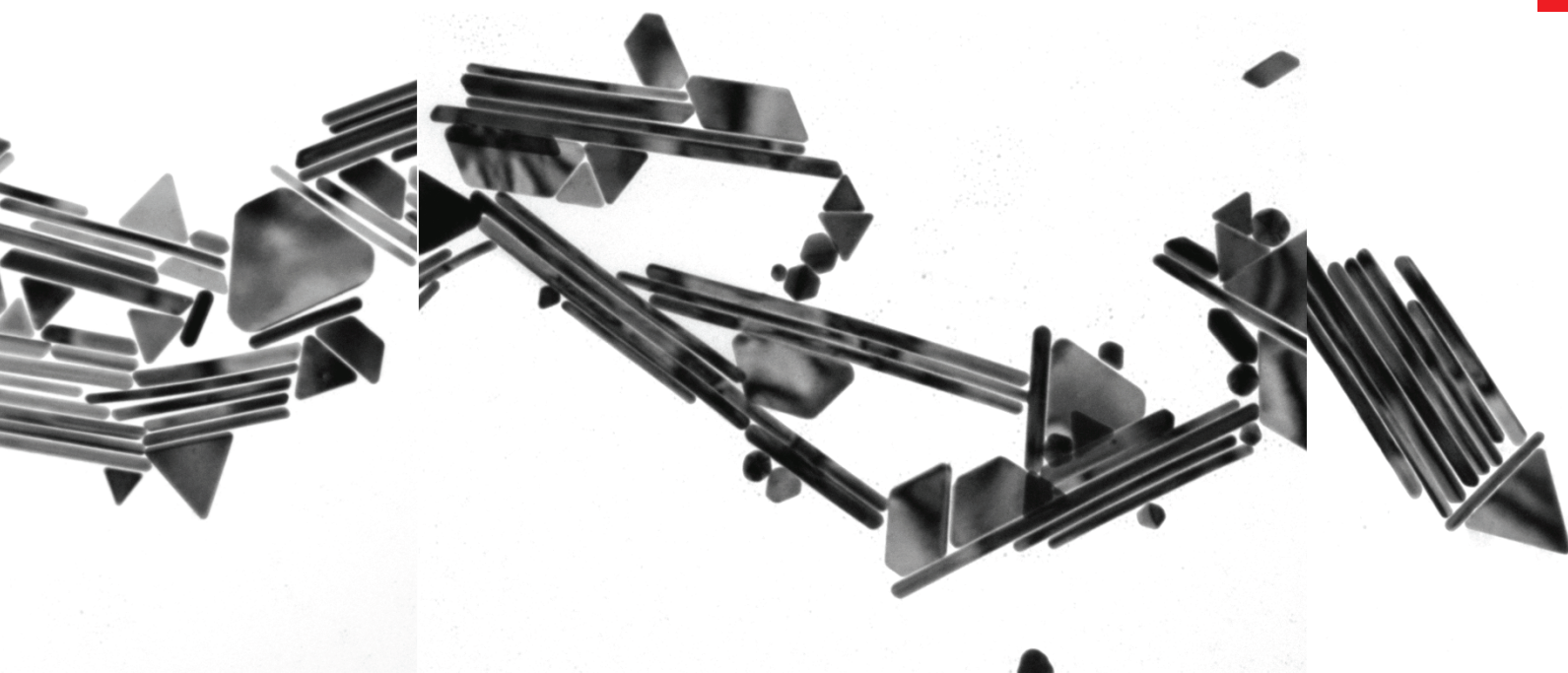
The success of multimodal therapy appears very promising. A review was



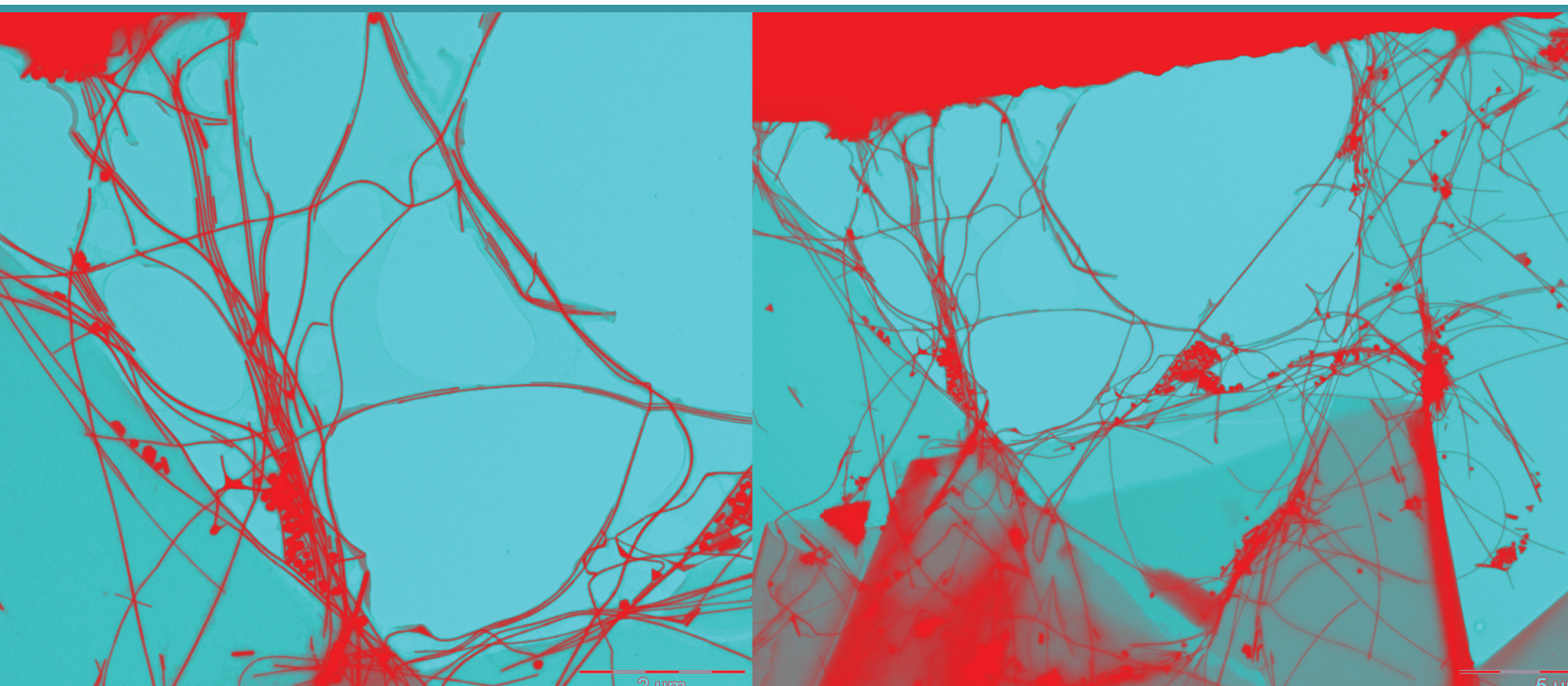
published by Yu Mi and co-workers in the journal *Nanomedicine* [21]. Successful examples are the following: a poly(lactic-co-glycolic acid) (PLGA) NP formulation of paclitaxel injected *in vivo* at doses of 10-mg/kg allowed 168 h of sustained chemotherapy treatment compared with only 22 h for the same dose of the free drug Taxol®. Similarly, the poly(lactide)-d- α -tocopheryl polyethylene glycol succinate (PLA-TPGS) NP formulation of docetaxel was able to do an even better job than the free formulation Taxotere®, with more than 15 days of sustained chemotherapy compared with only 24 h for Taxotere. Additionally, the latest progress in molecular biology has led to the identification of various selective ligands that could be conjugated onto the NP surface to target the delivery, mainly antibodies and aptamers [22, 23]. In another successful example, Wang et al. developed NPs with a hydrophobic cholesterol core, to uptake poorly water soluble drugs, and coated with a cationic polymer shell, to strongly attach to cell membranes, for the co-delivery of paclitaxel and

a cytokine, the interleukin 12-encoded plasmid. The *in vivo* synergistic anticancer effect was demonstrated in a breast cancer model in mice. It showed that the tumour growth rate in mice treated with paclitaxel-loaded NP/IL-12-encoded plasmid complexes was significantly lower than that in the mice treated with either of the therapies alone [24]. Besides, Sengupta and colleagues developed a variation of the previous, with a lipid shell composed of PEG-distearoylphosphatidylethanolamine, phosphatidylcholine and cholesterol, and a poly(lactic-co-glycolic acid) (PLGA)-doxorubicin-conjugated polymer core [25]. These NPs were subsequently loaded with combretastatin for a combination of chemotherapy and anti-angiogenesis therapy with encouraging results.

Hence, it would be possible to create a nanocarrier that contains, for example, a molecule to hide the Drug Delivery System from the immune system, a ligand that promotes uptake by specific cells, and the drug which, in turn, can be attached via



a responsive link which releases it only after a specific response such as a pH drop. The core of NP conjugates can also act as an effector in radiotherapy. Thus, AuNPs are stimulating new research as radiosensitisers due to the induction of an Auger cascade after an ionising event localised in the vicinity of the AuNP surface and a more than expected efficiency [26]. These special properties open up the possibility to strategies that use AuNPs as a carrier and effector.



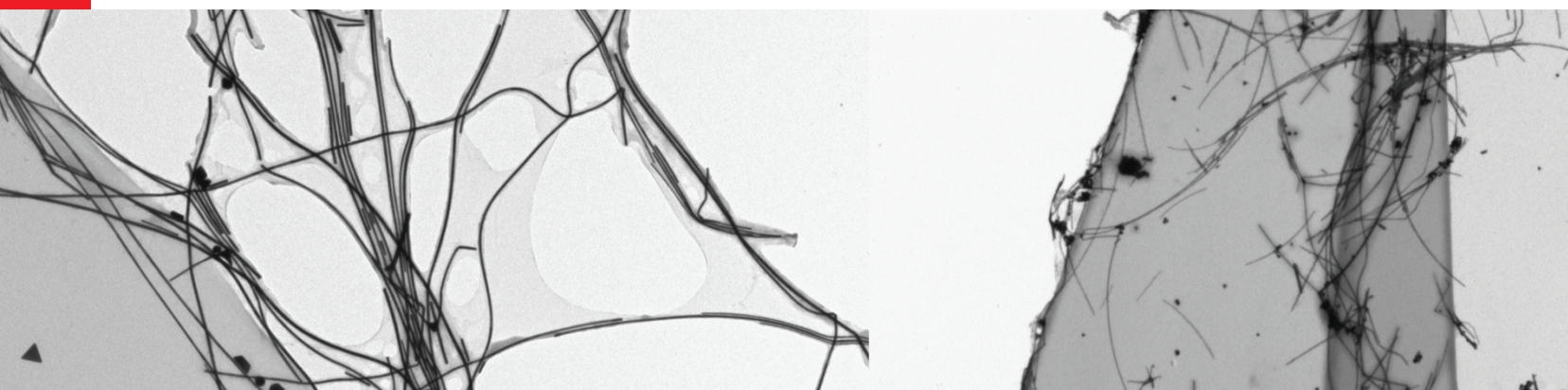


BIODISTRIBUTION

One of the most fascinating effects of loading or conjugating a nanoparticle and a drug is how the biodistribution of that drug is altered. By associating the drug to the NP, its physicochemical fate is modified, and in fact, it is the properties of the NP and the conjugate that determine the fate (pharmacokinetics and biodistribution) of the carried drug. Thus, nanocarriers can strongly contribute to modifications in pharmacokinetics and biodistribution, by driving the drug through different pathways, depending on the physicochemical properties of the nanocarrier (e.g., size and surface charge); this is especially appealing in the case of very toxic drugs [27, 28]. The fate of the drug and the vehicle will also strongly depend on the portal of entry, either injected (intravenously, intramuscularly, peritoneally), via the gastrointestinal tract, via the respiratory system or through the skin.

In fact, delivery has to be understood at three levels: body, organ, tissue. Imagine an NP intended to treat cancer which is injected in the vein. First,

it has to travel through the systemic-lymphatic system towards the target organ, let us say the lung. Once it reaches the lung, the NP has to find the affected tissue and sub-organ localisation of the tumour, and once the NP has reached the tumour, it has to deliver its cargo to the tumour cell. Of course, the needs and conditions for travelling in different regions are very different. For example, in the first case, one would like to have small, hydrophilic highly circulating particles to ensure that the tumour is reached without immune, hepatic or renal clearance. However, these super-travelling properties are no longer required once the carrier has reached the target (indeed, now we want it to travel no further, but instead penetrate and remain while performing their task, before they are destroyed, or their travelling abilities are recovered for expulsion). Once it is accumulated in the target organ, the carrier has to find the target cell. Conjugation of antibodies or aptamers specific to tumour cells may play a role in the uptake of these NPs by tumour cells. It is worth noting here

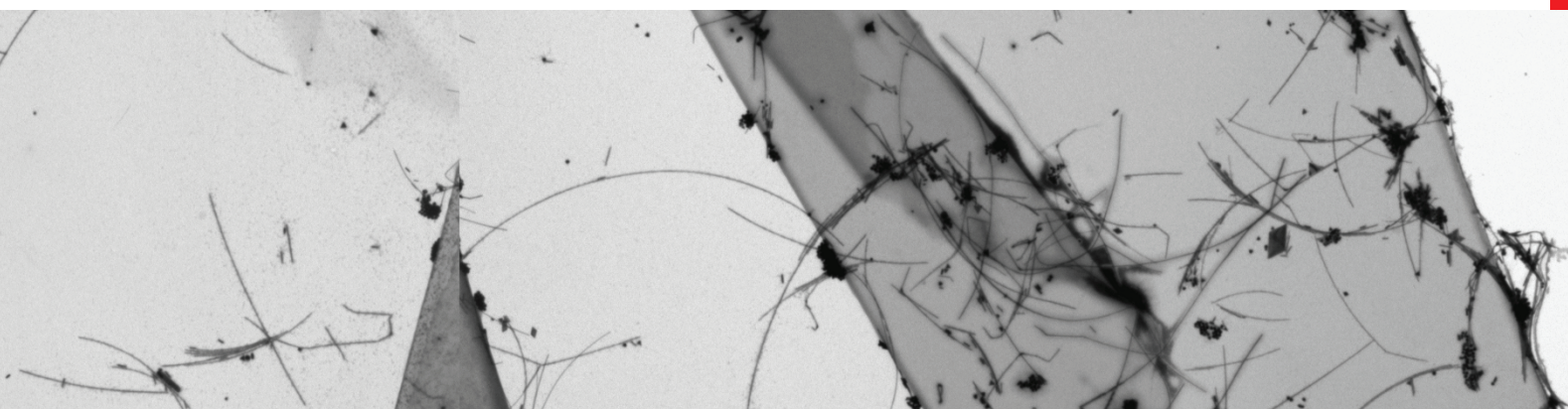


that the so-called directed nanoparticles (NPs with specific ligands) may induce confusion about their role in directing the NP (and drug) towards its target. It is widely accepted that the physicochemical properties of the system (mainly size, and surface charge) determine the primary distribution of those NPs independent of the presence or absence of ligands. On the other hand, the presence of ligands may play a role favouring uptake by specific cells once the NPs arrive at the target. This fact has to be taken into account when translating promising *in vitro* results to *in vivo* experiments. A great uptake by cells in *in vitro* experiments will not be relevant if the target is not reached before.

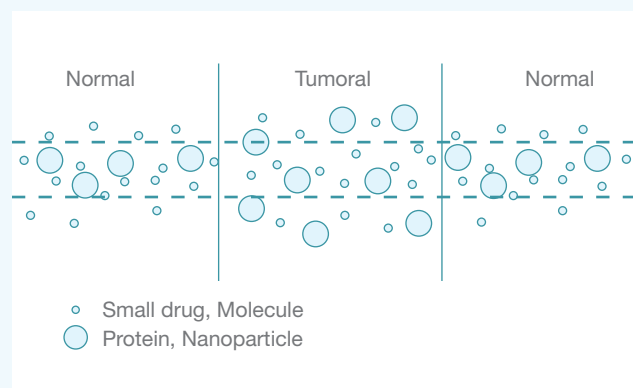
PORES INSIDE THE BODY

SMALLEST CAPILARY:	6 μm in diameter
SMALLEST CELL:	3 μm Sperm Cell
LARGEST CELL:	15 μm Ovule
PLATELETS:	3 μm
RED BLOOD CELLS:	5 μm
WHITE CELLS:	10 μm
PORES OF TIGHT JUNCTIONS:	< 1 nm
PORES OF CONTINUOUS CAPILLARIES:	< 6 nm
PORES OF FENESTRATED CAPILLARIES:	< 50-60 nm
PORES OF SINUSOIDAL CAPILLARIES:	< 100 – 1000 nm
PORES OF TUMOR BLOOD VESSELS:	< 200 – 600 nm
PORES OF THE NUCLEAR MEMBRANE:	< 8-9 nm
PORES OF THE CYCLOSKELETON:	< 20 nm

Inside the body, once the NP enters the systemic system, it will encounter pores that are smaller than 1 nm in the tight junctions of certain continuous capillaries (including the central nervous system, i.e., the blood-brain barrier, placenta and testis barrier), while other continuous capillaries (muscle, lung, skin) have pores of 6 nm [29]. Fenestrated capillaries (intestine, some endocrine and exocrine glands) have pores of up to 50–60 nm, usually closed by a diaphragm [29]. Finally, discontinuous capillaries (liver, spleen, bone marrow) have pores between 100 and 1000 nm, which allow the passage of macromolecules between the plasma and interstitium [29]. Thus, small molecules (below 6 nm, such as the majority of drugs, water, salts, amino acids...) leak in-and-out from the blood vessels and can be rapidly (in minutes) cleared via the kidneys [30], while the passive transport of macromolecules through these pores is negligible. Thus, an NP sized between 6 and 40 nm may follow *protein paths* to finally accumulate in organs of the mononuclear phagocyte system, especially the liver and spleen, as do proteins and protein aggregates [31]. Larger size NPs are easily recognised by the immune system and may also end up in the liver and spleen, but within a shorter time and in a different way (after phagocytosis) [18]. In all cases, surface modifications allow the modification of this size-dependent fate, for example, by making small NPs recognisable by the immune system [32]

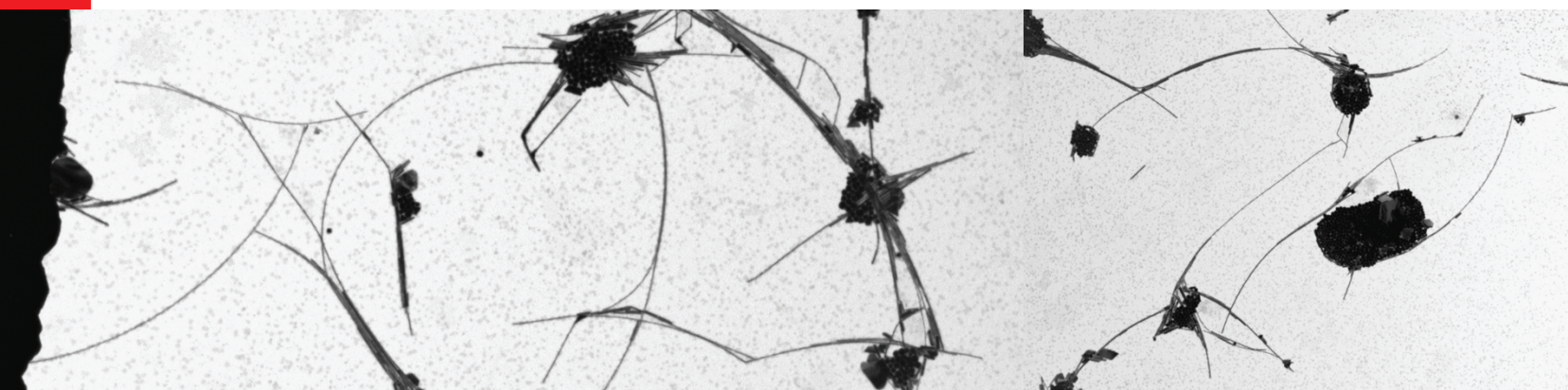


or shielding the large ones by means of chemical modification such as PEGylation [33]. It is worth noting here that blood vessel permeability changes in diseases such as inflammation and cancer [34]. During inflammation, blood vessels grow large pores to allow cells of the immune system to extravasate from the blood into inflamed tissue. In cancer, the rapid growth of tumours results in leaky vessels surrounding it. These fenestrated vessels allow macromolecules and NPs to permeate through the tumour. In addition, the nanoparticles are retained there due to the lack of a functional lymphatic system. This effect (the above-mentioned Enhanced Permeability and Retention effect, EPR) is widely reported in the literature [35, 36] and has been exploited to passively accumulate nanocarriers in tumours [5].



Scheme showing the differences of the vascular system of normal and tumour tissue. Leaky vessels and non-functional lymphatic system are responsible for the passive accumulation of NPs in tumours.

This effect, first reported by Matsumura and Maeda [37], exploits the ability of NPs to permeate through the leaky tumour vessels (with fenestrations between 100 and 800 nm [28, 38]) and to be accumulated into the tumour due to the lack of a functional lymphatic system. Long-time circulating NPs maximise the EPR effect since the changes required to permeate through the tumour vessels are greater. Related to this, the size of NPs plays an important role in determine tumour accumulation and distribution: 60 nm AuNPs showed a greater accumulation than 20 nm AuNPs, likely due to a faster accumulation and slower clearance. However, larger AuNPs are accumulated in the perivascular region of the tumour failing to penetrate deeper, whilst 20 nm AuNPs were still found to be significant 50 μm from the blood vessel [38]. This intrinsic property of NPs to be passively accumulated into tumours has been exploited to deliver a great variety of drugs [4]. Some groups proposed further improving this accumulation by attaching a ligand that is recognised by receptors overexpressed in tumour cells. These include epidermal growth factor (EGF) [39], folate [40] and transferrin [41], amongst others. However, there is some controversy regarding the efficiency of this approach [42]. It is not clear whether active targeting favours accumulation in the tumour, since physicochemical properties of NPs govern these pharmacokinetic properties of Drug Delivery Systems. Thus, the



size and surface charge and composition (e.g. presence of stealth agents or not) of NPs seems to play a more important role in determining the final distribution of the Drug Delivery Systems [27], while ligands influence only interactions directly onto the cell once it has been reached (e.g. a greater uptake). Besides, strong interaction with peripheral cells may sabotage tumour penetration. Of course, ligands show an amazing behaviour in *in vitro* models where there is only the nanocarrier, salts and serum and the target cell in the experimental well.

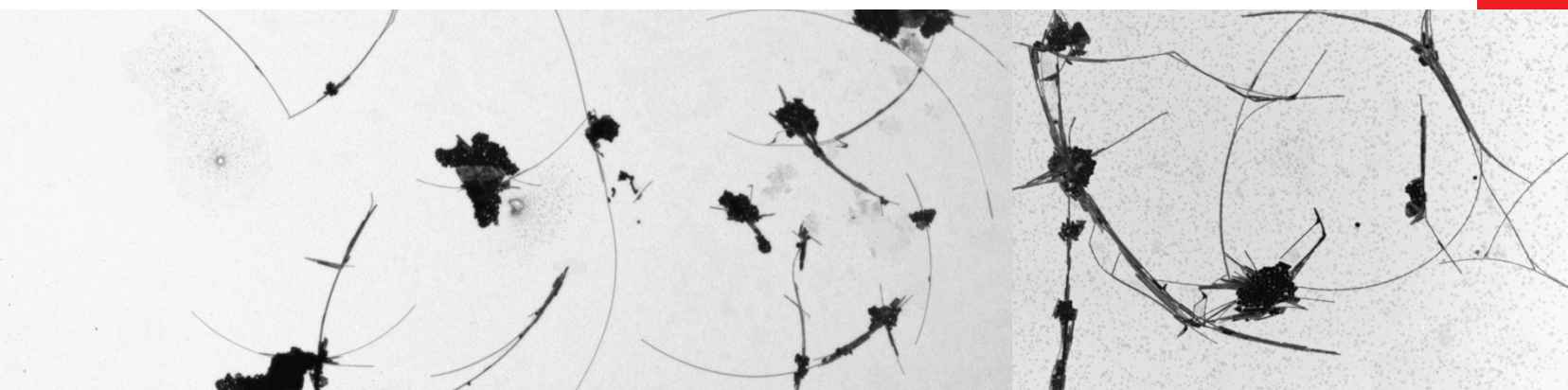
FATE OF NANOPARTICLES INSIDE THE BODY.

Summarising, in contrast to small drugs, nanoscale objects travel following particular paths through the body [29, 35].

This results in the passive accumulation of nanocarriers in:

- i. Organs of the mononuclear phagocyte system [31] (such as the liver, spleen and bone marrow), where blood vessels are fenestrated with gaps ranging between 100 and 1000 nm.
- ii. Inflamed tissue, where an increased permeability is achieved through temporal induced gaps to recruit immune cells [34].
- iii. Solid tumours, in which its rapid growth results in leaky vessels [38]. These fenestrated vessels allow macromolecules and NPs to permeate through the tumour. In addition, the nanoparticles are retained due to the lack of a functional lymphatic system. This effect (EPR) is widely reported in the literature [35, 36] and has been exploited to passively accumulate nanocarriers in tumours [5].

As demonstrated, it is important to choose appropriate NPs since the pharmacokinetics and biodistribution of the conjugates will be governed by the physicochemical properties of the carrier rather than by those of the drug [27]. In addition, EPR effect is known to be size dependent. It is not enough that the NP is smaller than the pore; this also depends on the Brownian motion and positioning of the NP in the blood stream, which for the most part is a well-organised laminar flow where small objects tend to go towards the centre of the stream with respect to larger ones, as expulsion from the highest force gradients is more efficient in large objects. Indeed, cells are accordingly distributed by size, with the white ones being found outside, platelets found in the centre of the stream, and red blood cells in between. Thus, for example, it has been reported that 20 nm PEG-coated AuNPs showed the best behaviour for tumour treatment since they present a high accumulation rate due to their long half-life in blood and an acceptable penetration in the tumour. On the other hand, larger NPs (>40 nm) failed to penetrate deep into the tumour and were only accumulated at the vicinity of the vessels [43]. Smaller NPs, which would have penetrated deeply, did not have the opportunity to be significantly accumulated in the tumour due to renal clearance. Of course, different materials with different surface characteristics and administered in different forms will travel to different



locations despite having the same size. Obviously, these properties would have been modified if colloidal stability had been compromised, showing again the importance of maintaining NP stability along the process, and avoiding aggregation and sedimentation.





DRUG DELIVERY

Today, dosing, despite being recognised as fundamental for centuries (*sole dosis facit venom* Paracelsus said in the XVII century), it is still quite rudimentary. As in the “magic bullet” concept, one would like to both customise bullets (e.g., therapeutic cocktail) for each patient and only dose target areas and target cells. Instead, we dose by age, body surface and body weight. Therefore, it is expected that biomedicine will be more adapted and directed in the future, optimising dosing and decreasing side effects, thus maximising therapy. For this task, nanoparticles are especially suited.

THE MAGIC BULLET

In the XIX century, Paul Erlich postulated the idea of the magic bullet (*magische Kugel*), an ideal therapeutic agent: a compound that selectively targeted a disease-causing organism, so that a toxin for that organism could be delivered along with the agent of selectivity. This was initially phrased against infectious organisms, but also applies to cancer cells.

Delivery of therapeutic molecules to the target inside the living body is a challenging task.

The progress of drug development is nowadays limited since most of the delivery methods are based mainly on oral or injection delivery routes, which strongly determine the formulation of the drugs. Precise drug release into highly specified targets involves miniaturising the delivery systems to become much smaller than their targets.

Nanoparticle drug delivery systems, due to their small size, may penetrate across barriers through capillaries into individual cells, to allow efficient accumulation at targeted locations in the body. A wide variety of engineered NPs have been extensively used or are currently under investigation for drug delivery. The employment of NPs for the delivery of pharmaceuticals can result in higher concentrations than possible with other drug delivery methods, which could enhance the drug bioavailability or dosing at the targeted site as well as the overall efficiency of the used drug. For example, the involvement of stable conjugates of

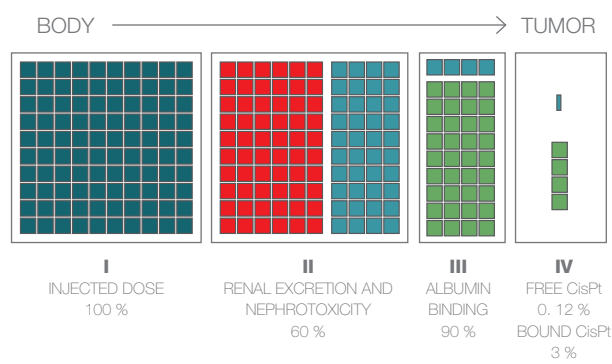


AuNPs coated with antibiotic molecules for therapy increase the efficiency of drug delivery to target cells in some studied cases. Injecting patients with gold may sound like an expensive option, but with thousands of nanoparticles fitting into the width of a human hair, the amount of metal used is miniscule. Gold, unlike some other metals, is not toxic and has been used in various medical treatments for many years without any observed harmful effects.

Note the normal evolution of a drug inside the body looking at the example of cisplatin, where only 1-2% of the administrated drug reaches the tumour. After intravenous injection, up to 60% is filtered by the kidneys in a few minutes, where the majority of the side effect damage is localised. From the remaining 40%, 90% of it irreversibly attaches to albumin. The albumin cisplatin conjugate accumulates in the organs of the Mononuclear Phagocytic (immune) system, such as the liver, spleen and bone marrow, as well as the tumour via EPR (*vide infra*). The free and still active cisplatin distributes homogeneously through the body, as small molecules do. Therefore, 2-3% of the initial dose of cisplatin can be found in the tumour. In addition, the dose of the active drug is even lower, since most of the drug is attached to albumin. Unfortunately, the one bound to albumin is useless, but this already indicates that vehicles are interesting; if it can be released from the albumin in the tumour, the effect would be

great. Albumin-cisplatin complexes do not go to the kidney, therefore preventing the production of well-known cisplatin side effects [17]. The advantages of encapsulation of the drug and its delivery are that this minimises side effects by preventing uncontrolled dispersion (carpet bombing), and protects the drug during its journey, allowing a decrease of the administered doses, improved efficacy and decreased side effects (increasing efficiency), improving therapy.

DOSING THE BODY OR THE CELL: THE CASE OF CISPLATIN.



Fate of injected cisplatin inside the human body. The distribution of a drug inside the body only allows for a small portion of it to reach the target, and from this, only a little will not have been deactivated in plasma, as in the example of cisplatin.



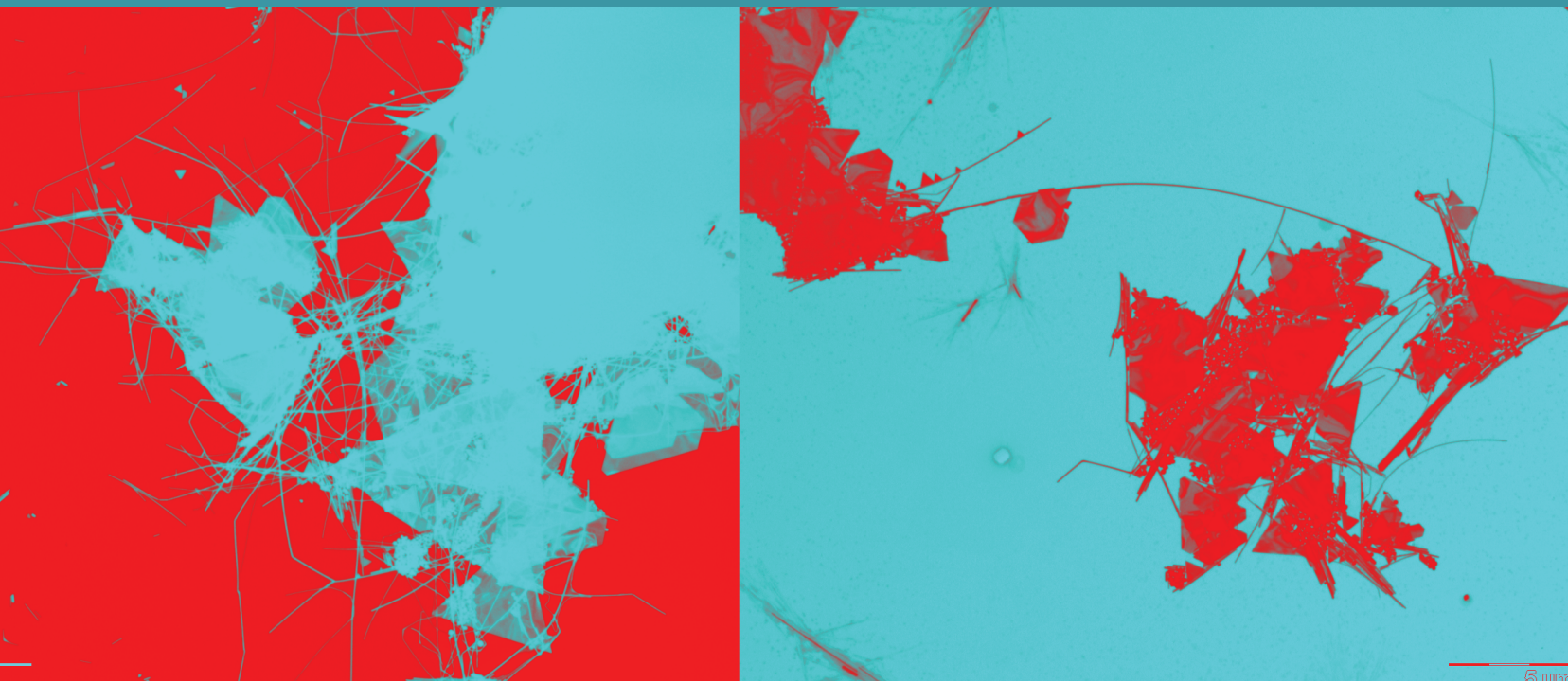
Advantages of NP-mediated drug delivery also include the ability to reduce toxicity and the systemic side effects of the drug, as well as the **loading of therapeutic agents into systems that are shielded from the immune system**. For instance, Tumour Necrosis Factor (TNF) directly bound to AuNPs has been shown to be less toxic and more effective in reducing the size of a solid tumour growing in mice than native TNF, due to the fact that maximal anti-tumour responses were achieved at lower doses of the drug [44]. Because of their suitable size (10 to 100 nm), inorganic NPs are often taken up by cells where larger particles would be excluded or cleared from the body by rapid phagocytosis, as with microspheres; this is a clear advantage of small carriers. For example, the typical blood clearance time of 300 nm polymer particles was a few minutes, while smaller particles of 10-20 nm had a lifetime in the blood of a few hours to several days. Also, the change in particle size from 240 to 80 nm showed an extension of the half-life of the particles in mice and the drug within (TNF) by about 24-fold from 28.2 min to 11.33 h. Thus, in laboratory studies, a reduction of toxicity of a very effective drug that is still limited by its side effects, without affecting its efficacy, has often been observed [17].

Moreover, NPs have the advantage of the **ease of synthesis with high monodispersity**

ranges; some are simpler and some are more monodisperse. A good example is gold, where the high monodispersity and ease of production coincide. Also, gold is useful due to the **ease of functionalisation and the possibility of multiple conjugations** with a variety of molecules with different functions [45]. In these systems, the inorganic core imparts stability to the assembly, while the molecular monolayer allows tuning of surface properties such as charge and hydrophobicity/hydrophilicity. Finally, many inorganic NPs possess unique chemical, optical and magnetic properties, making it possible to **track their trafficking and localisation with subcellular resolution**.

These novel properties make inorganic NPs very appealing delivery vehicles for the pharmaceutical industry since they may provide life-cycle extension of drugs close to patent expiration or new reformulations of drugs, to reduce side effects and increase patient compliance. In addition, innovative carriers may make it possible to use certain drugs which previously did not fulfil the required criteria for toxicity or administration and failed in advanced trial phases. Thus, in addition to improving its solubility, protecting it, and transporting it to the tumour, the large size of the conjugate avoided unwanted dispersion in tissues such as the heart, where the blood vessel pores are approximately 6 nm (50

KDa). This would help to improve the efficiency of the treatment since classic therapy often has to be stopped before the end of the prescribed regime due to toxicity issues. All of the data indicate that, thanks to reduced toxicity, if cumulative toxic effects are avoided, this will allow continuation of the treatment for longer times or to change the strategy of administration.



BIODEGRADATION AND EXPULSION

Still, biodegradation and expulsion, together with full ADME (Administration Distribution Metabolism and Expulsion) of the carriers from the body is one of the major unknown areas in some of the proposed nanoparticles.

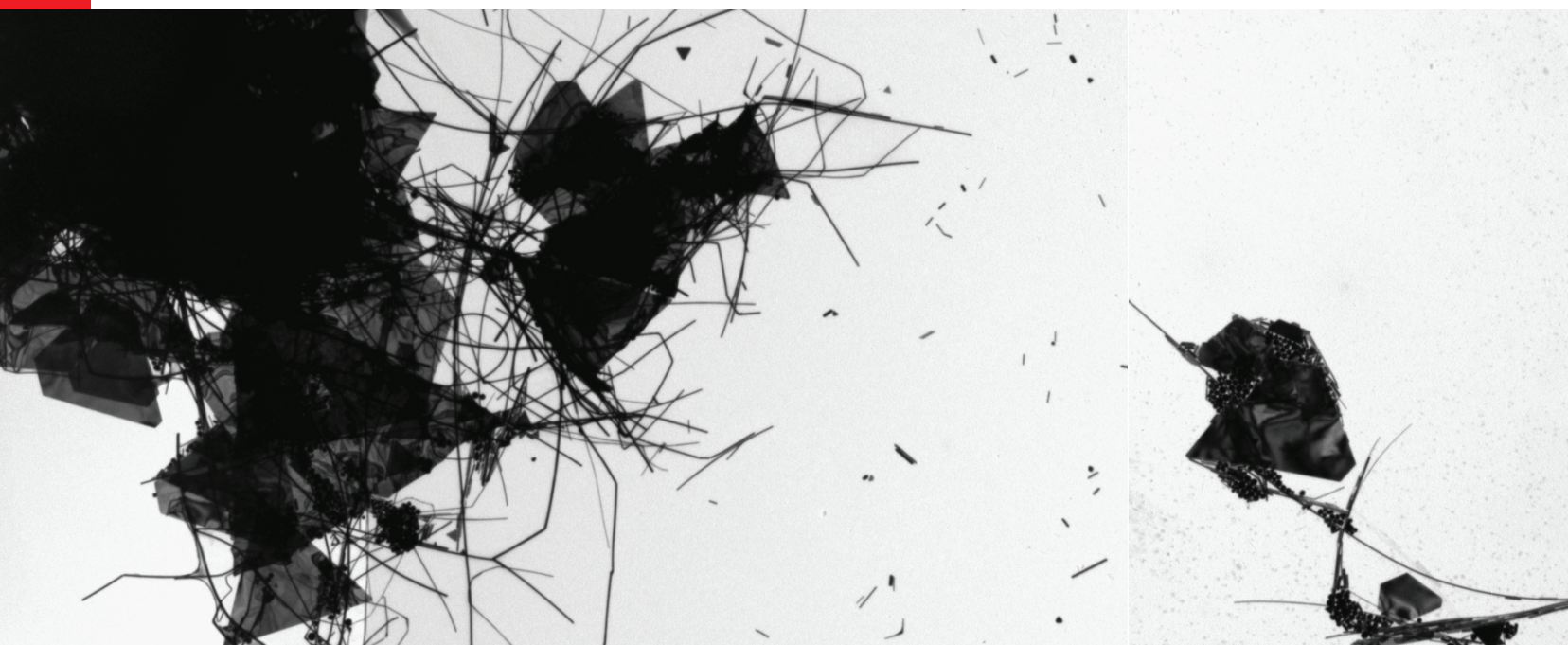
Despite the good development of implants, the chronic pulmonary inflammation produced by asbestos and silica (asbestosis, silicosis) has raised concerns about the potential effects of NPs inside the body, as they could also produce a similar size-related effect as non-biodegradable materials. However, it has been repeatedly observed that objects less than 10 micrometres are phagocytosed and removed from the body, avoiding the setting of chronic inflammation, as is the case for non-biodegradable nanoparticles bigger than 20 μm [46].

Traditionally, drugs have been designed to be small, with some hydrophilic characters for solubility, and some hydrophobic ones to enable crossing the cell membrane and thus reaching targets inside the

body. These principles are known as Lipinski's rule. This ensures that the drug will arrive to the target, but for the same reasons, this cannot prevent the drug from travelling everywhere inside the body, which is the cause of many undesirable side effects. Small molecules, salts and amino acids constantly enter and exit the blood stream and the lymph, while larger ones have more constraints to freely move across the body. Thus, for small molecules (below 6 nm) the body is a liquid phase with solid particles inside, like a *noodle soup*. For larger molecules, proteins, nanoparticles and others, the body is a soaked solid structure with some liquid highways and reception organs.

LIPINSKY RULE OF 5

- No more than 5 hydrogen bond donors, (nitrogen or oxygen atoms with one or more hydrogen atoms).
- Not more than 10 hydrogen bond acceptors, (nitrogen or oxygen atoms).
- A molecular mass less than 500 Daltons.
- An octanol-water partition coefficient log P not greater than 5.

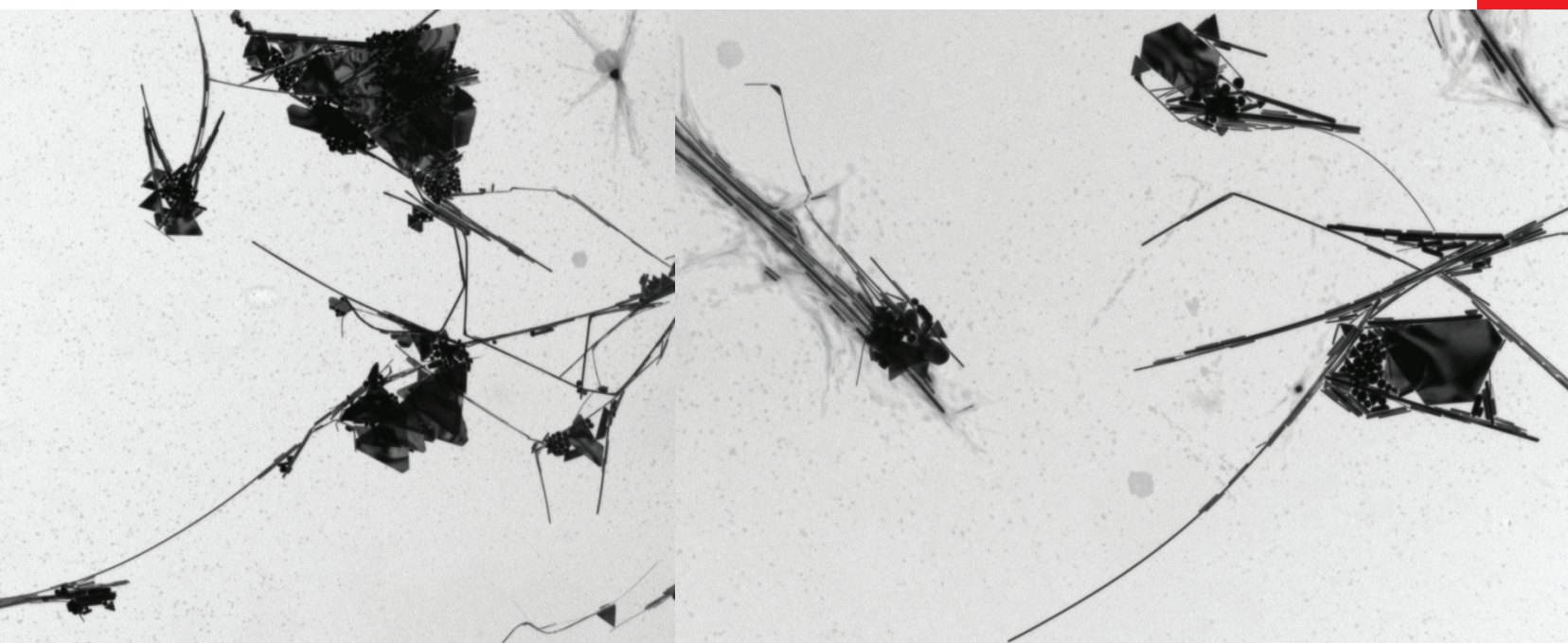


This is of special importance in the case of anticancer therapies in which the widespread distribution of small molecular chemotherapeutic drugs is often limiting treatments due to severe side effects that make it impossible to reach the full benefits of the therapy. Molecular drugs are small enough to travel through the body along with ions and small nutrients due to the selective permeability of continuous capillaries for ions and small molecules [29, 34]. This results in a high index of permeability and distribution through the whole body, intended to allow the active principle to reach its target [47, 48]. Unfortunately, this widespread distribution of the drug is at the origin of unwanted side effects, causing low drug selectivity and efficiency [49]. As an example, the severe nephrotoxicity induced by cisplatin is a dose-limiting factor and, in many cases, the treatment must be stopped before therapeutic benefits are reached. In addition, this is a reason to prevent its use in patients with renal insufficiency. Therefore, to avoid uncontrolled dispersion, many conventional

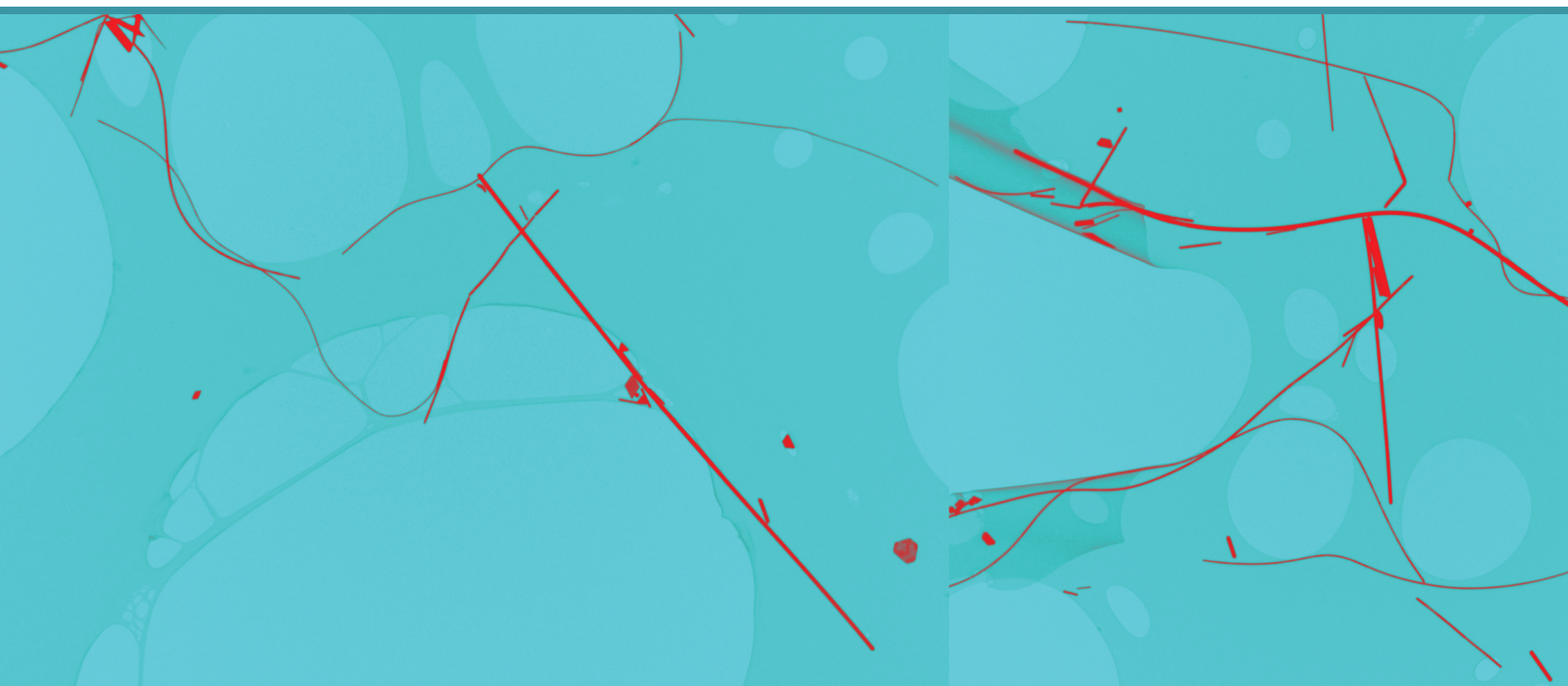
therapies can be improved by size through the use of Drug Delivery Systems.

Once the NPs reach their target with their therapeutic load, different strategies have been used to release the drug. Normally, the strategies are based on the different physicochemical properties found in the cytoplasm compared to the extracellular environment (e.g. blood). For example, NPs are known to be internalised via endocytic pathways, in which a pH drop is produced [50]. Thus, a pH-sensitive link between the drug and NPs ensures the non-specific release of the drug during circulation through the body [17]. A controlled release can be also achieved by the reduction of an oxidised inactive prodrug in the cytoplasm, releasing the drug in its active form [51]. Also one can take advantage of specific enzymes to cleave the link between the NP and the drug [52].

Liposomes and iron oxide nanoparticles are known to be degraded into innocuous phospholipids



and iron salts, respectively. However, at higher concentrations of iron oxide, or in the case of more robust materials such as gold, accumulation and persistency has been observed where slow hepatobiliary excretion of the carrier has been reported. Interestingly, as mentioned above, this had an impact on the regulation of the use of nanoparticles, thus, iron oxide nanoparticles, injected in the tumour by the gram and which remain there, have been regulated as a device, as an implant that allows medical treatment (hyperthermia), while blood-circulating iron oxide nanoparticles, which slowly provide Fe^{2+} ions and finally dissolve into iron salts, have been regulated as a drug.

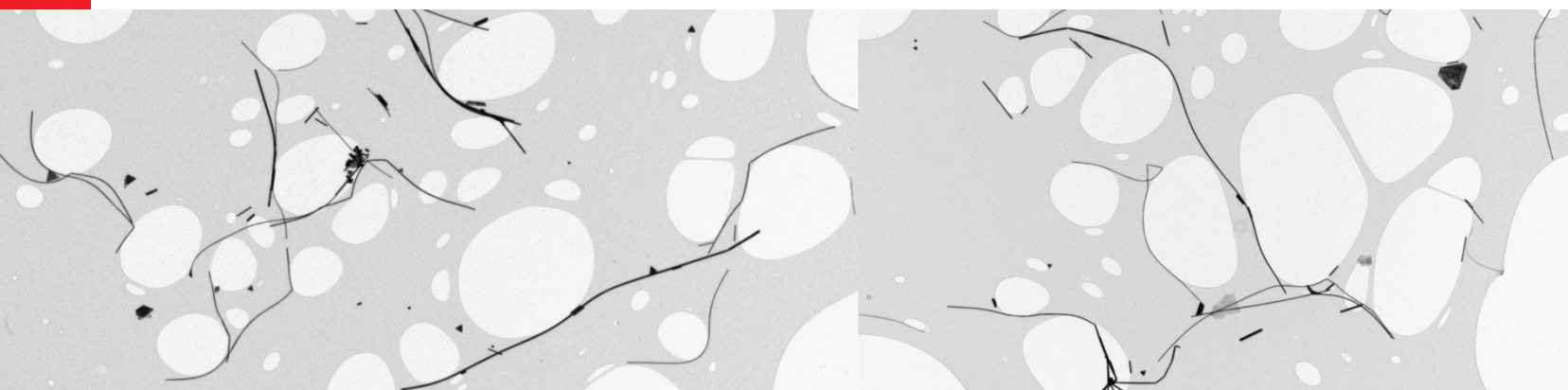


THE REMAINING CHALLENGES

Despite this good news for nanomedicine, there are still a few barriers to cross that will determine the success of the field. If today's trials lead to better medicines, we expect a revolution in medical treatment using nanotechnology, while a failure of the current initiatives may drive investment and translation away from the field of nanotechnology. For example, novel carriers will have to be studied closely for potential toxicity. Fortunately, experience with liposomes can be used as an advantage and *versions of* gold nanoparticles have also been used safely for many years. To treat rheumatoid arthritis, gold salts, such as aurothiomaleate, have been used. Inorganic compounds that have Au^{1+} in the formulation indeed, but gold in any case, can be reduced to metallic AuNPs in the cellular environment. It is interesting how, depending on the redox potential of the material, its fate in the body can be so contrasting. On the one hand, materials with higher redox potential, the potential of a substance to be in its oxidised or reduced state, compared to those found in the body, tend to be

mineralised inside the body, as gold, or by humic acid, as silver. Also, when the redox potential of the material is lower than the biological one it will encounter, the nanoparticles tend to be corroded as iron oxide nanoparticles.

Thus, despite the large number of NPs, organic or inorganic, and conjugated chemotherapeutic agents which have shown promising results in the laboratory, the precise behaviour of these conjugates *in humans* is still rather unknown, with controversy about disparities between the *in vitro* and *in vivo* results or results from different laboratories. There are indications that small modifications of the nature of the NPs and NP conjugates have a strong influence on conjugate interactions [53], protein corona formation [54], aggregation [55], degradation [56], and consequently different biological behaviour during their full life cycle inside the body [57]. This indicates the great versatility and enormous potential of nanotechnology to access the biological machinery.

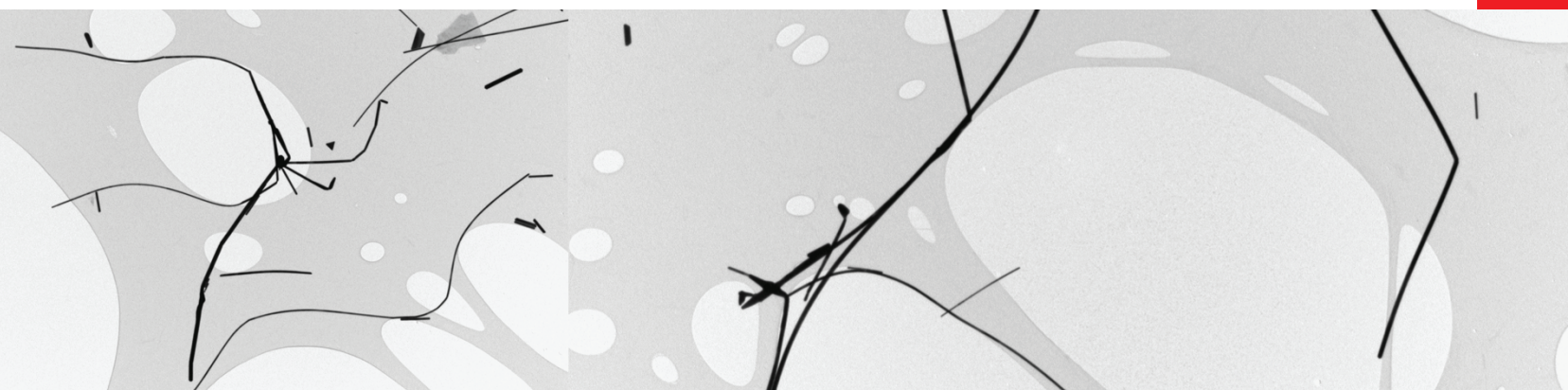


As a consequence, reproducibility and morphology control has to be strict since small variations in the formulation may have dramatic consequences in *in vivo* experiments and final applications, both medical and others.

Another issue that every nanocarrier has to deal with is the penetration into tumours. It is known that macromolecular carriers (and nanoparticles) fail to penetrate deep into the tumours and are generally accumulated just some micrometres away from the vessels [27, 38, 58, 59] that transported them, surrounding the tumour. This could be used to remove, as by hyperthermia, the fibrosis coating the tumour before surgery [60]. However, there is a greater accumulation of active drug when attached to NPs, as the drug is protected against deactivation by plasma proteins, and a possibility of successive treatments, if toxicity is clearly reduced; these factors may overcome the lower penetrability of the vehicles [58], allowing, for example, the progressive erosion of the tumour in longer treatments.

After terrible drug toxicity due to minute modifications of the atomic configuration, as in the case of thalidomide or trans fatty acids, enormous pressure has been placed on quantum control of drug production, which has been translated to nanocarriers. Therefore, the **precision of**

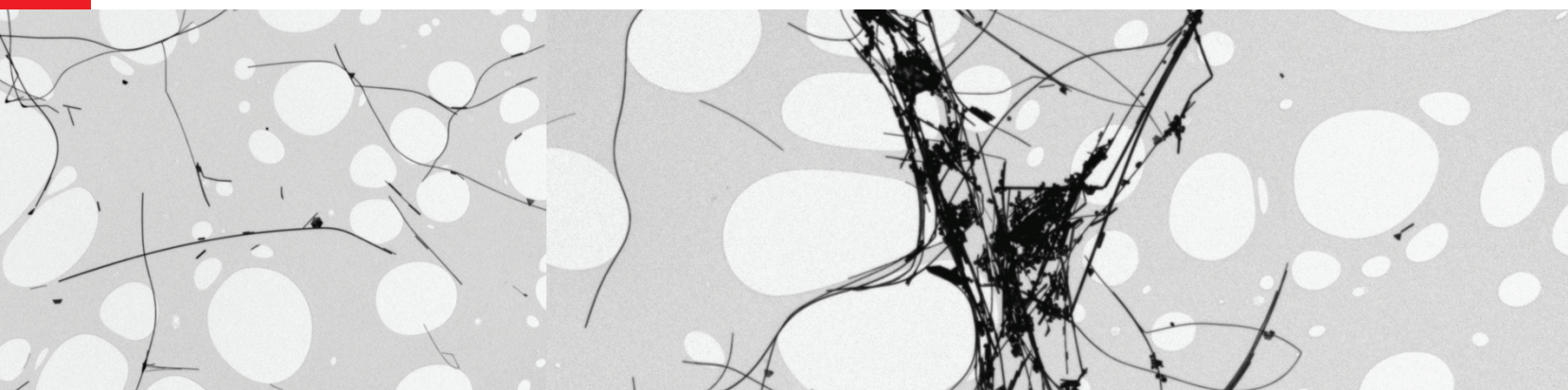
production, reproducibility and productivity are major barriers to developing nanomedicines, including delivery vehicles that have to be produced in appropriate quantities. A typical synthesis of NPs renders **concentrations** in the range of 10^{12} – 10^{13} NP/mL [61]; thus, NPs are typically synthesised at the nanomolar scale. This is because colloids (nanoparticle suspensions) are naturally out of equilibrium: the nanoparticles do not float, they sink, but this is so slow and dispersed by Brownian motion that they seem to behave, at our scale, for extended times, as a homogeneous solution. That is to say, small NP (less the 100nm) colloids macroscopically behave as soluble substances; however, they are physically disperse and tend to minimise surface energy when this is possible, either via adsorption of molecules or aggregation. Therefore, they are more stable at low particle concentrations. Otherwise, NPs tend to aggregate and sediment. Even though high densities of loading have been achieved [62, 63], the as-synthesised concentrations of drugs onto NPs will rarely be higher than 10 micromolar. Taking into account that there is a limitation of the volume that can be injected into the body (e.g. 10 mL/Kg for intravenous injection in mammals), the therapeutic dose might not be reached unless NPs are previously concentrated.



This concentration step is not always straightforward because the concentration of NPs can lead to **aggregation** if special care is not taken (e.g. the concentration of NPs without any surfactant increases the chance of aggregation), due to the intrinsic nature of the colloidal state, be it made up of inorganic NPs or proteins. Evidently, the special properties of NPs are lost if they aggregate. Therefore, in too many cases, the loss of colloidal stability is behind the lack of (or unexpected) biological responses [27]. Thus, one has to ensure the maintenance of colloidal stability along the process: synthesis – storage – exposure/treatment. It is common to assay the stability of NPs in storage conditions (e.g. in aqueous media) even if they are very different from the working conditions. However, biological fluids such as cell culture media or blood are complex mixtures of salts, proteins, sugars, etc. that may promote the destabilisation of NPs, and therefore stability should of course be assayed in the working conditions. The same consideration is valid for the stability of the bond with the drug. For example, cisplatin adsorbed on AuNPs, is not released in water, whilst it is non-specifically and quickly released in cell culture media. On the other hand, cisplatin linked via a coordination bond is stable in both media and is only released after a pH drop [62].

Additionally, the need for a certain concentration of NPs to reach therapeutic doses implies that a single lab-scale synthesis might not be sufficient to achieve the amount of NPs required to perform *in vivo* experiments. Thus, not only should **monodispersity** be guaranteed to control size effects, but reproducibility batch to batch should also be consistent. In addition, robust synthesis protocols are needed to facilitate the scaling-up of the production, which is essential for the transference of the technology to the industry and the clinic [64]. It is not surprising that the pharmaceutical industry appreciated the ability of small companies to produce NPs under industrial and regulatory standards, rather than their specific formulation.

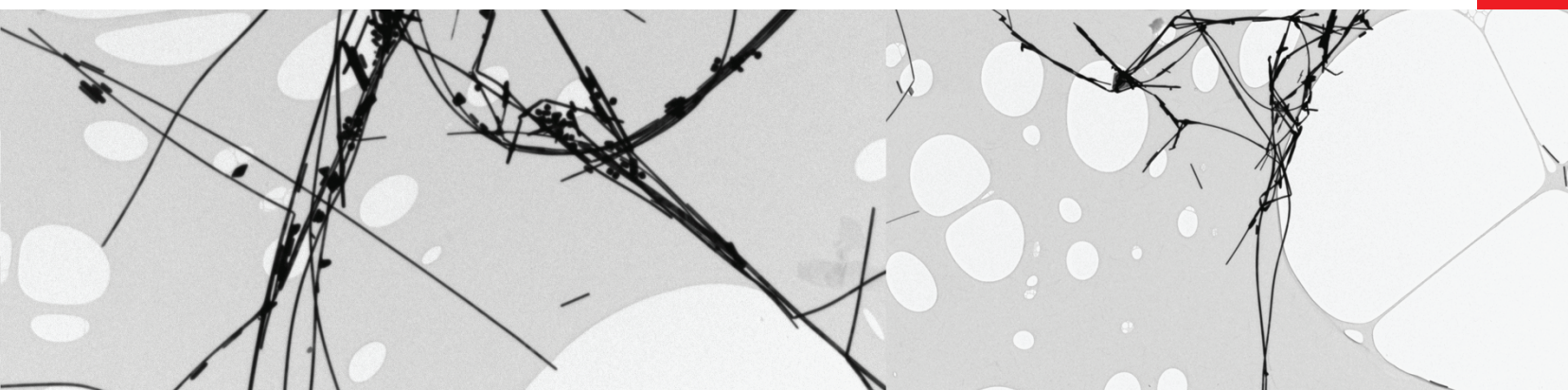
The choice of appropriate **models** to determine the potential therapeutic benefits is also not trivial, especially for new technologies in which the amount of literature is limited. Simple *in vitro* tests, such as those assessed in monolayer cell cultures, do not consider important factors such as tumour vascularity, tumour penetration and other differential properties given by the tumour microenvironment [65]. Consequently, 2D *in vitro* results do not necessarily reflect the behaviour of the assayed nanotechnologies in a real situation; this is especially true in the case of drug delivery vehicles that should travel through the body and



find the tumour before killing the tumour cell. In this context, 3D cell cultures have been proposed as models to study the behaviour of drugs in the particular environment of a solid tumour due to the possibility of having an extracellular matrix and different regions of a tumour (e.g. hypoxic cells in the internal areas). Since the advantages of using carriers are achieved mainly by modifications of the pharmacokinetic properties of the drug, *in vivo* models may be preferred, which implies the difficult choice of using animals since, among others, this raises ethical concerns. In addition, there is a great variety of tumour models [66], including xenografted, orthotopic, and spontaneously and induced autochthonous tumour models. These models show variations between them such as different sizes of pores in vessels or different immunological responses, which may result in different efficiencies for the same Drug Delivery System depending on the model used. Also, in order to work with animals with implanted tumours, SCID (Severe Combined Immunodeficiency) models are normally used, which lack a fully functional immune system. As discussed, due to the importance of the interactions between the immune system and nano-objects, this impedes observation of the real effects of nanomedicine and may provide as much false positive as negative data.

Control over the release of the drug is also a key

aspect. Ideally, the drug release is triggered by external stimuli which can be voluntarily applied to have total and controlled ability to dose the target cells in the target organs and no others. However, initially, the release patterns were close to those of the drop-by-drop technology: the capsule was releasing the drug as it was progressing inside the body. Additionally, an initial burst release was also observed, which could account for up to 40-50% of the encapsulated drug, minimising the effect of carrying. Nevertheless, such approaches succeeded to show better therapeutic profiles with less toxicity in some cases. In between, time- and environment-controlled release may be used, for example, if the NPs are cleared in hours from the blood stream, a capsule that takes longer to degrade may prevent systemic distribution of the drug, while the hypoxia and acidic environment of the tumour can be used for the NP to be activated and release its drug. Unfortunately, while the decrease of oxygen or the increase of protons are biologically dramatic, they are chemically less important; therefore, it is difficult to use these biological changes in the environment to produce strong chemical changes in the carrier. Today, finer adjustments are being developed, as the enzymatic cleavage of the linker can leave the drug and NP joined. Normally a compromise has to be reached: if one wants to ensure that no unspecific release is produced, then the bond between the NP and the drug, or



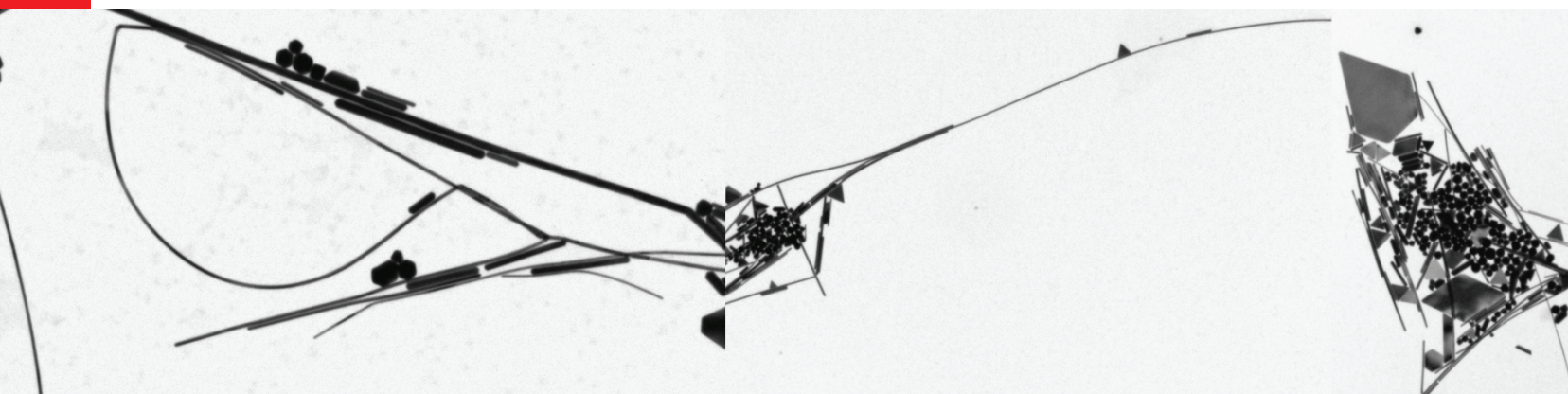
the robustness of the capsule, have to be strong and high enough that there is no significant release except where desired. In some cases, drugs carried by nanoparticles were observed to produce non-toxic effects, or therapeutic ones; simply, the drug was never released from the NP inside the body. Fortunately, if the carrier is endocytosed, as seen for objects smaller than 100 nm and larger than 2-3 nm, then the environment suffers a radical change with pH decreases of two orders of magnitude or more (even below pH 4 in the late endosomes and endolysosomes), which is a significant chemical change. Other proposals are to combine the thiolated drug with a 1-2 nm AuNP that will cross the cell membrane and reach the cytoplasm, where the presence of glutathione will compete with the drug for the NP surface, provoking the cytoplasmic delivery of the drug [67].

Another issue which should be studied is the expulsion of NPs from the organism since this might influence **long-term toxicity**. This is a part of something fundamental we have yet to learn: the

full pharmacokinetics, biodistribution and ADME (Administration Distribution Metabolism/Degradation Expulsion) of NPs. In general terms, it seems clear that small NPs (<6 nm) are rapidly excreted by kidney filtration. For example, more than 80% of 4 nm quantum dots were found in the urine 4 hours after injection [30]. However, glomerular filtration in kidneys is ineffective for larger NPs. Then, the preferred route of excretion is through the faecal matter, via the hepatobiliary clearance route [68]. This excretion pathway is much slower, and long-term (up to two years) accumulation of AuNPs, but not Fe₃O₄, has been observed in mice [69]. The second are known to dissolve in *in vivo* conditions. Thus, NPs which are larger than 6 nm not only increase their blood half-life, avoiding renal clearance, but also show a greater accumulation in organs of the RES (reticuloendothelial system), increasing the likelihood of toxicity in these organs. Therefore, the absence of toxicity in the long-term in liver and spleen, among other organs, has to be ensured for NPs that are not cleared by kidneys.

KEY WORDS IN PHARMACOLOGY

Efficacy	The ability of a drug to produce the desired therapeutic effect.
Efficiency	The ability of a drug to produce few or no side effects while still performing its work.
Pharmacokinetics	How the body affects a specific drug after administration. <i>What the body does to the drug.</i>
Pharmacodynamics	The study of biochemical and physiological effects of drugs on the body. <i>What the drug does to the body.</i>



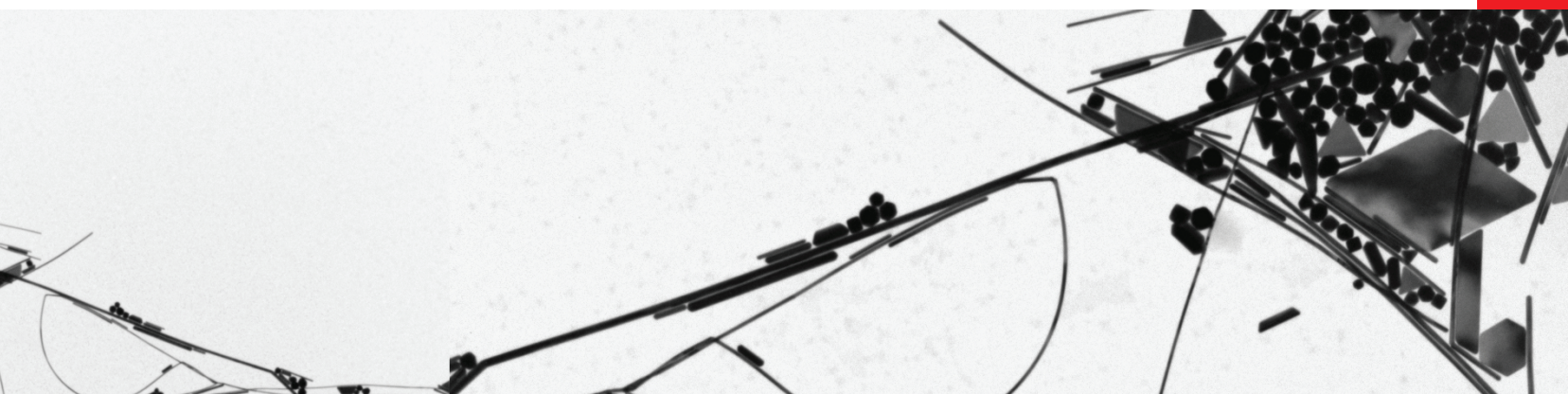
The Immune System Challenge.

Once the NPs come into contact with the body, of significant importance is the **interaction of NPs with the immune system**, also known as the reticulo-endothelial system or mononuclear phagocytic system, because one cannot put substances inside the body without asking the immune system for permission. Thus, to test the possible side effects of NP compounds, *in vitro* and *in vivo* assays are normally performed on murine models. Those assays are generally focused on studies of the effects of NP compounds on antigen presentation and adaptive immune response as well as innate immune response, which are important arms to be considered in immunology.

In fact, the immune system is designed to fight against commensal organisms that invade the body, and the signals coming from them. Thus, the immune system detects proteins, with sizes ranging between 6 and 30 nm, and distinguish self from non-self; it also detects larger entities, such as protein aggregates and viruses, and much larger

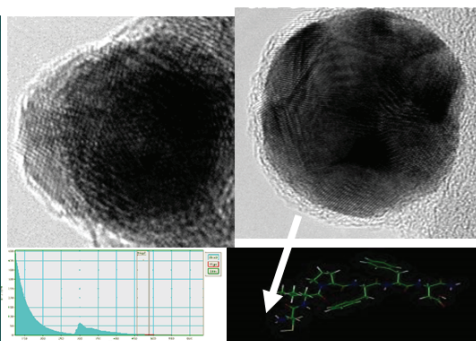
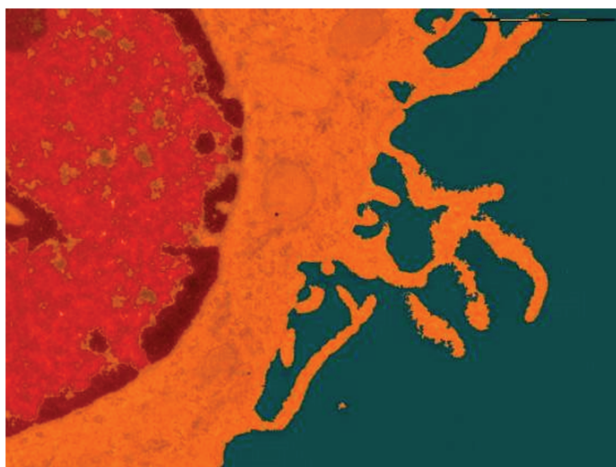
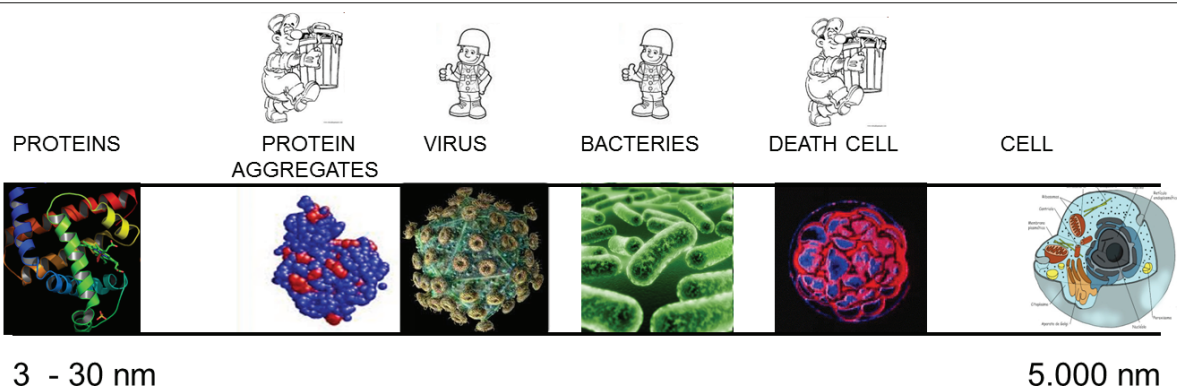
bodies such as cell debris or prokaryote cells. Once the immune system detects a strange object: i) it may be tolerated and allowed to pass, as is seen for self and healthy proteins and cells, ii) it may be recognised as wrong and removed, with the immune system acting as a trashman, without conflict, or iii) it may be categorised as an invader and trigger inflammation. The immune system removing the nano-object may be disappointing when this object is the carrier of a drug destined for another location. Also, the induction of inflammation may be very deleterious for the host. Therefore, understanding these interactions, or what has been called nanoimmunology, is of great importance.

The model response of the immune system to exogenous materials will thus serve to understand the behaviour of NPs in the body, specifically to determine the ability of NPs to interfere with the pathways involved in the presentation and cross-presentation of foreign antigens by Dendritic Cells, as well as the role of NPs on their activation



status upon lipopolysaccharide (LPS) and CpG (bacterial specific DNA sequence) challenge. It is also important to assess the role of chronic NP treatment on the immune system. It is also important to determine the ability of both T- and B-cell subgroups to respond to antigen challenge.

IMMUNE RESPONSE TO THE CONJUGATES



Au-cysLPFFDNH2

Bastus et al ACS nano 2009, 3, 1335



Toxicity.

When using a new vehicle, the study of its **toxicity** is mandatory. As scientists have been assessing the biological impact of individual nanomaterials in various biological systems, it has been observed that, regardless of the biological assay, most NPs are not obviously toxic, and those that do have an observed toxic action, often only manifest this at very high concentrations. However, literature on environmental pollution and well known cases of asbestosis, silicosis, sarcoidosis and others, stress the need for precaution when using engineered NPs. This observation demands that more attention be focused on understanding what makes some specific particles toxic (e.g., particles which are positively charged [70, 71], release toxic ions [72], carry toxic chemicals [73] or biologically active agents [74], or aggregate to large dimensions able to cause frustrated phagocytosis [75-77]).

Possible adverse effects of NPs such as acute toxicity and long-term accumulation should not be underestimated and should be studied on a case

by case basis. There is some controversy regarding the *in vivo* toxicity of NPs and the parameters that play a role in NP-induced toxicity [31]. Some studies have found no toxic signals after the administration of NPs [78], small alterations in the biochemical markers due to metabolism of the NPs or indications of temporal inflammation [79], while many other have shown no adverse effects when discarding simple contamination and NP aggregation [77]. On the other hand, it is believed that the dysfunction of major organs may be related to the presence of NPs at the site of abnormalities. For that reason, there are a lot of studies regarding toxicity in the spleen and liver, which are generally accepted to be the organs with the highest accumulation of NPs. Liver toxicity, when found, seems to be associated with a hyperplasia of Kupffer cells that induces acute inflammation with an influx of neutrophils [80]. This acute inflammation is a transient response to the insult of NPs; however, apoptosis and necrosis of hepatocytes as well as accumulation of NPs could be related to toxic



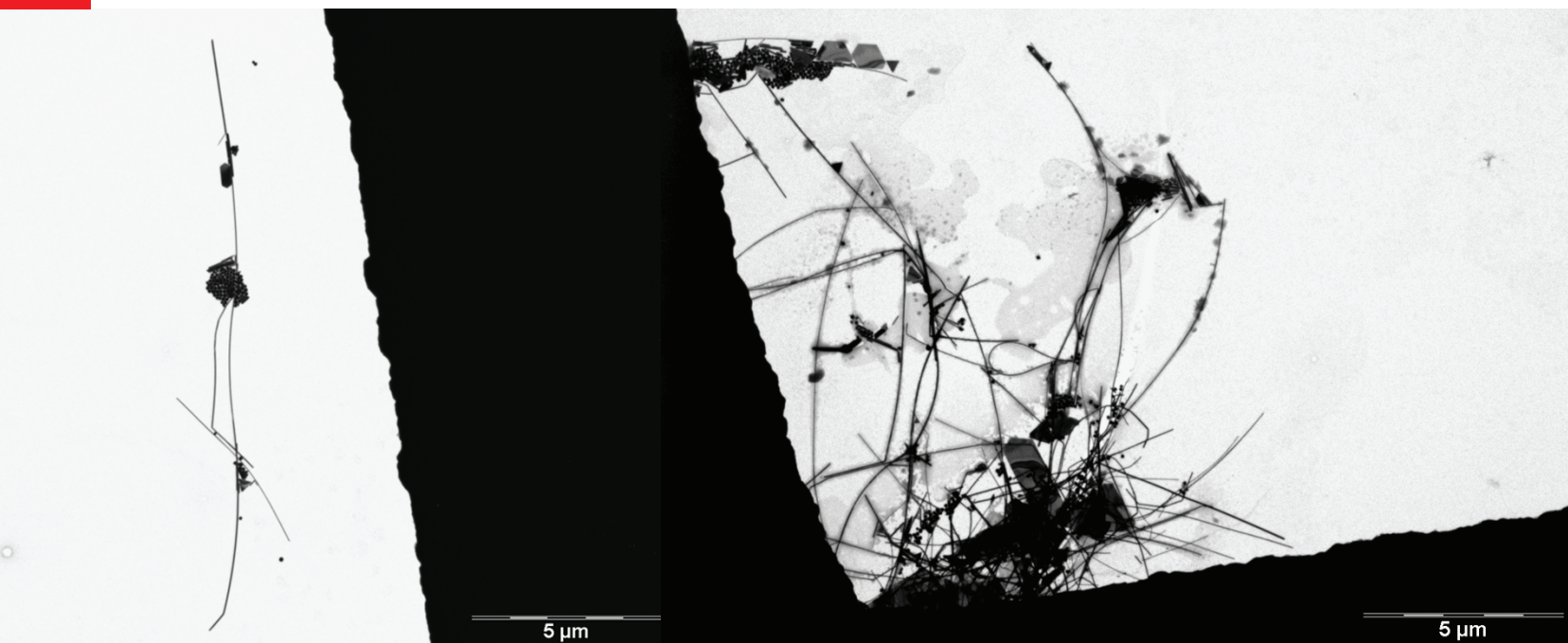
effects [81]. Regarding the spleen, macrophages of the periphery seem to be involved in the uptake of NPs by this organ, thus leading to a temporal inflammation of the spleen. White pulp aberration has been also observed [82]. Additionally, in other cases, a loss of weight has been observed after intravenous administration [79]. However, it seems that these toxic effects are related to known toxic moieties within the NPs, excessively high (not realistic) concentrations or aggregations. Thus, NPs can be produced in such a way that once they reach the liver, they are excreted via the bile. Still, long-term, sub-toxic accumulation and chronic exposure responses have not yet been determined, and are of relative importance in the case of cancer.

In this context, especially relevant is the question of subtle perturbations that are not observed in conventional *in vitro* toxicity studies, and the long-term exposure effects in healthy and challenged conditions, which can be multiplexed (combined exposures, depending on bioaccumulation and persistence of the produced effects), have to be investigated in a Risk/Benefit framework. It is important to remember here how the reward system in science management is so that it forces the publication of positive results at expenses of negative ones. However, the negative ones may be even more important than the positive ones to produce significant advances; that is to say,

one cannot easily prevent colleagues from doing something which is wrong and that will not work (which is somehow beautiful since one has to study the mistake until creating a positive piece of knowledge, and this enables the understanding of the mechanisms behind the studied phenomena, but is terribly inefficient). Many times, it is better to know what not to do rather than what to do. Animals are often pointlessly sacrificed, the efforts of young people is wasted and public money is irresponsibly spent because the negative results are not made public consistently ("this approach, at this concentration, or under these conditions, does not work").

ADVANTAGES OF NANOCARRIERS

- i. Possibility of multiple functionalisations which allow combined therapy.
- ii. Promote a double effect by acting as carriers and as effectors.
- iii. Increase the solubility of poorly soluble drugs in plasma.
- iv. Protection of the drug from deactivation.
- v. Promote endocytosis of the drug.
- vi. Serve as contrast agents to monitor treatment.
- vii. Increase blood half-life of the small drug.
- viii. Accumulate in the tumour via the EPR effect.
- ix. Reduce toxicity in normal tissue.
- x. Encapsulate large quantities of therapeutic agents.
- xi. Control release of the drug directly to the site of action.
- xii. The cargo effect is useful to overcome drug resistance.

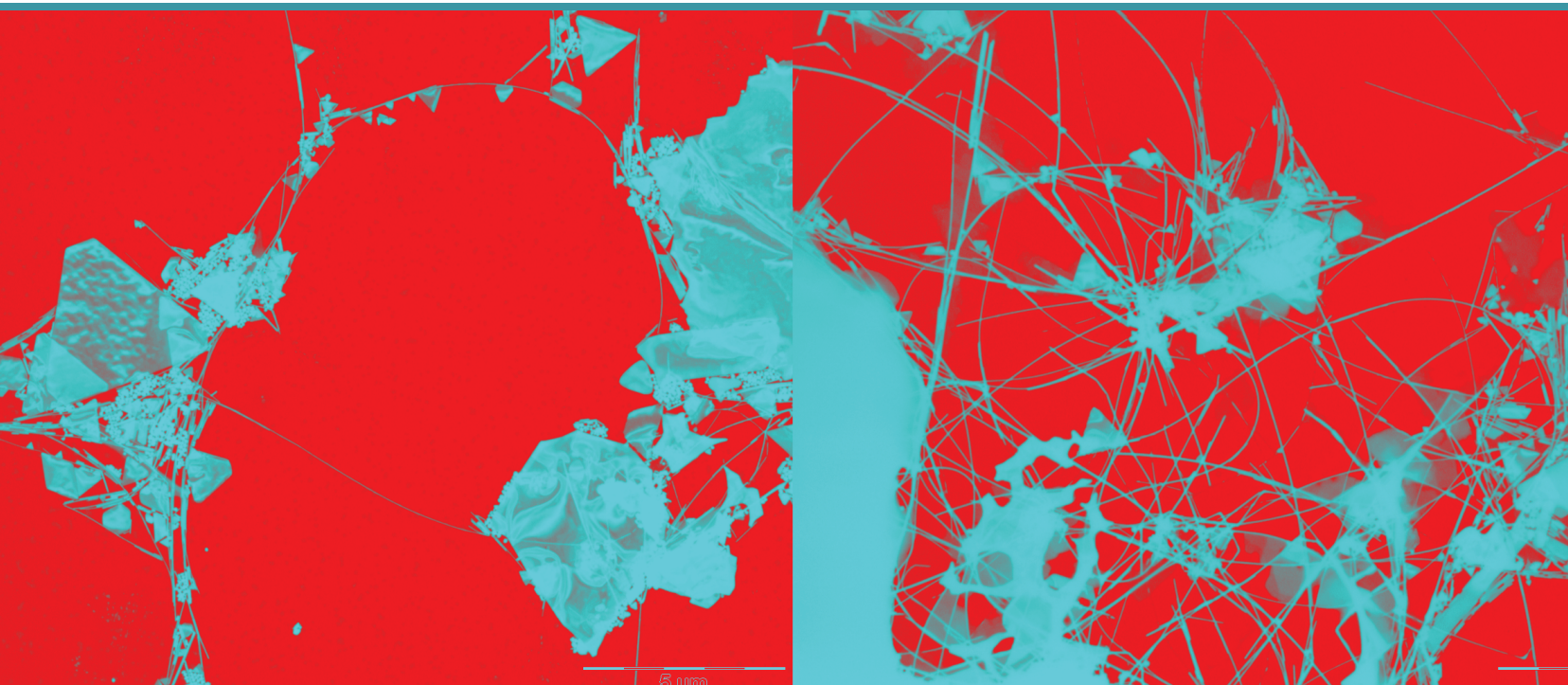


ADVANTAGES OF NANOPARTICLES

- i. NPs possess **unique physicochemical signatures** that allow their easy detection in biological environments.
- ii. NPs are **Drug Delivery Devices**. They are drug cargos (a high dose of drug arrive at more delayed and intermittent times) and modify the biodistribution of the drug in the organs, in the tissues and in the cell. They protect and retard drug release and favour endocytosis.
- iii. They are antennas that can absorb photons of a determined wave length and become excited in biological transparent environments. **NPs allow the remote and local (at molecular level) injection of energy.**
- iv. NPs allow the **fine-tuning of the conjugated molecule activity** thanks to: cooperative effects between the molecule and the NP, as in catalysis (the electron cloud of the NP may modify the reactivity of the attached molecule, modify its pKa, its catalytic activity...), absorbing molecules onto NPs allow for their tertiary structural conformation modification (and thus modify enzymatic activity), packing molecules protect them against degradation, and neighbouring molecules may also show cooperation.

In conclusion, some general trends can be extracted from the current literature, but it is clear that there are certain parameters that have to be taken into account before using NPs as a vehicle for medical applications: i. Size of the vehicle, since this will determine the clearance rate and the biodistribution [82]; ii. Surface composition, as it has been seen that changing the surface composition of NPs can change the biological behaviour [83]; and iii. Dose and administration route obviously play a role in the potential toxicity. Therefore, for every NP-conjugate, a pharmacokinetic study must be done to prove their usability in medical applications.



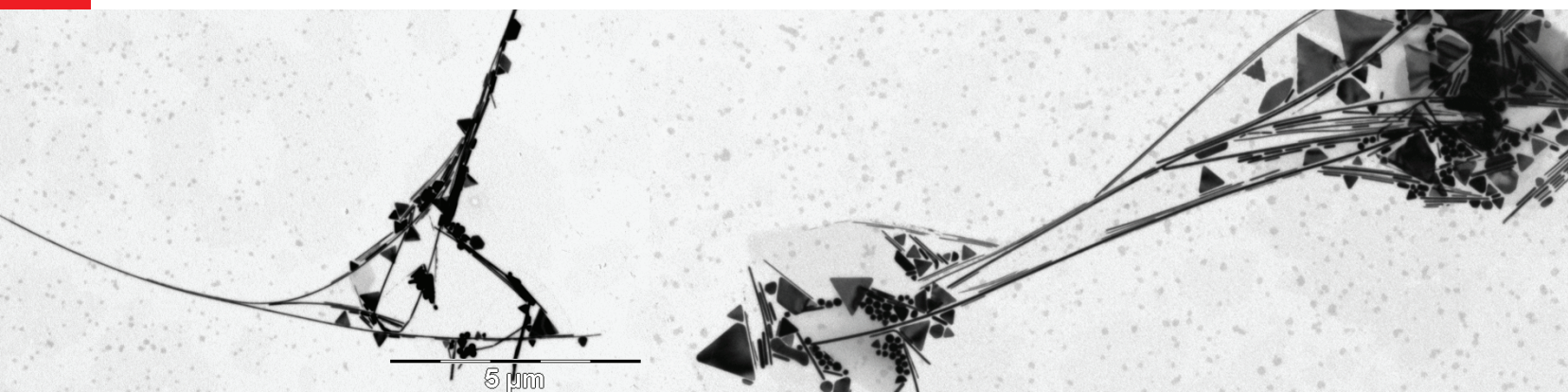


AN EXAMPLE: DETOXIFYING ANTI-TUMOUR DRUGS. THE CASE OF CISPLATIN

A representative example is CisPt carried by Au [17]. Recent efforts have been focused on targeting the tumour by using drug delivery systems to avoid the organs to which cisplatin is toxic. As the kidney is responsible for filtration and removal of molecules smaller than 50 kDa from the blood, which corresponds to molecular sizes of around 6 nm in diameter, any larger delivery vehicle will divert the drug away from the kidney [30]. Additionally, NPs accumulate in the tumour due to the EPR effect [35, 36]; which is known to be strongly size-dependent [38, 43]. Therefore, when the target is a solid tumour, nanometre-sized carriers are expected to be passively accumulated on it. This case also applies when cisplatin is bound to albumin. More than 50% of the administered cisplatin is known to bind irreversibly to albumin [84] and then reach the tumour by EPR; however, this form of cisplatin is inactive and has no biological effect [85]. Thus, a properly designed nanocarrier will not only transport cisplatin to the tumour, but will also protect it against plasma deactivation.

In this context, approaches based on the encapsulation and transport of cisplatin have emerged. Sterically stabilised polymeric nanoparticles, which have excellent stability in plasma, a much longer circulation time, better efficacy, and lower toxicity than free cisplatin, have been reported [86-89]. Such vehicles include lipid capsules [90] or polymers as in Prolindac®, which has a 22 kDa hydroxypropylmethacrilamide copolymer as a backbone and a pH sensitive glycine chelator linker [91]. Other examples include soluble CNTs [92], carbon nanohorns [93], and Fe₃O₄ NPs [94].

AuNPs have recently been proposed as scaffolds for cisplatin due to their controlled and reproducible synthesis and conjugation to cisplatin as well as the high loading of drug achieved [63]. Not only cisplatin, but other Pt derivatives, such as Pt (IV) prodrugs, have also been loaded on AuNPs with maintenance of the anticancer effect [95].



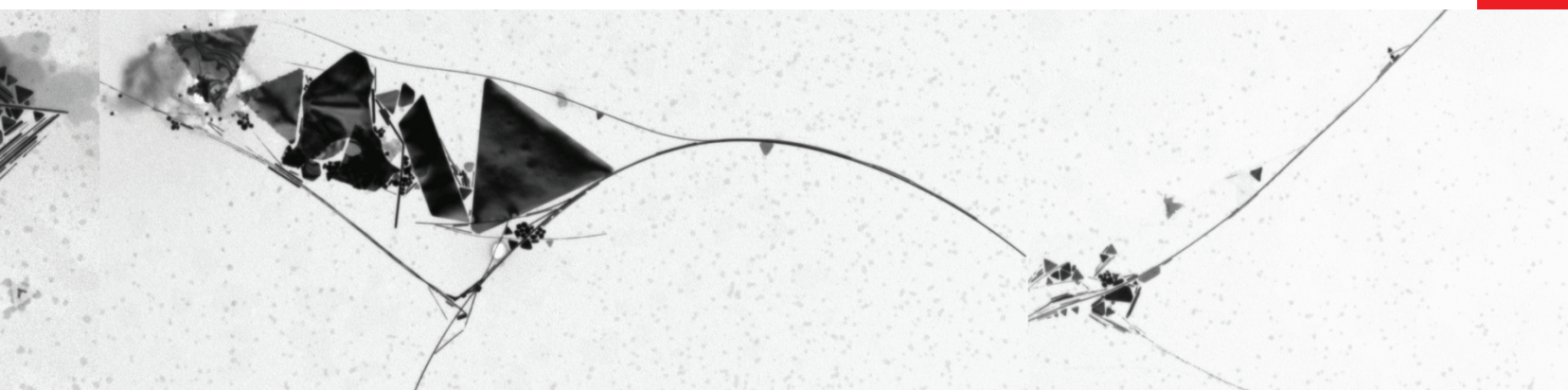
In closely related work, Ren *et al.* [96-98] reported the adsorption of commercial cisplatin to gold colloids via ionic interactions. Unfortunately, in the case of adsorption via ionic interactions on the surface of the nanomaterials, an uncontrolled rapid liberation of the drug was observed as soon as the conjugates are dispersed in highly ionic media such as serum [62]. In many of the reported systems, colloidal stability in the working environment was an issue.

Beyond oncology, small inorganic NPs the size of a small protein (5–30 nm) are making their way towards other applications in the clinic: AuNPs are used in cell imaging, targeted drug delivery, as photothermal agents for hyperthermia, and in other proposed diagnoses and therapies [99]. AgNPs display a biocidal effect that is currently applied in commercial products such as hospital equipment and devices. Magnetic NPs are present in various biomedical applications, *e.g.*, the early detection of cancer, diabetes, and atherosclerosis. CeO₂NPs are being used in biomedicine as an antioxidant to treat disorders caused by oxygen radicals, such as retinal degeneration or cardiomyopathy.

Finally, treatments with NPs are still very few and not beyond clinical trials. Thus, there is a lack of knowledge about regulatory aspects, since the traditional tests are not always adapted to

NPs and because the major effort on developing new technologies has been carried out by small companies, spin off and start-ups that lack the financing strength to carry fully extended regulatory preclinical and clinical studies.

In summary, many interesting results have been published on the conceptual development of vehicles for drug delivery; however, many aspects still need to be developed. Today, the tool is ready; now we need to discuss how this tool can be used to our advantage with those in the medical field.



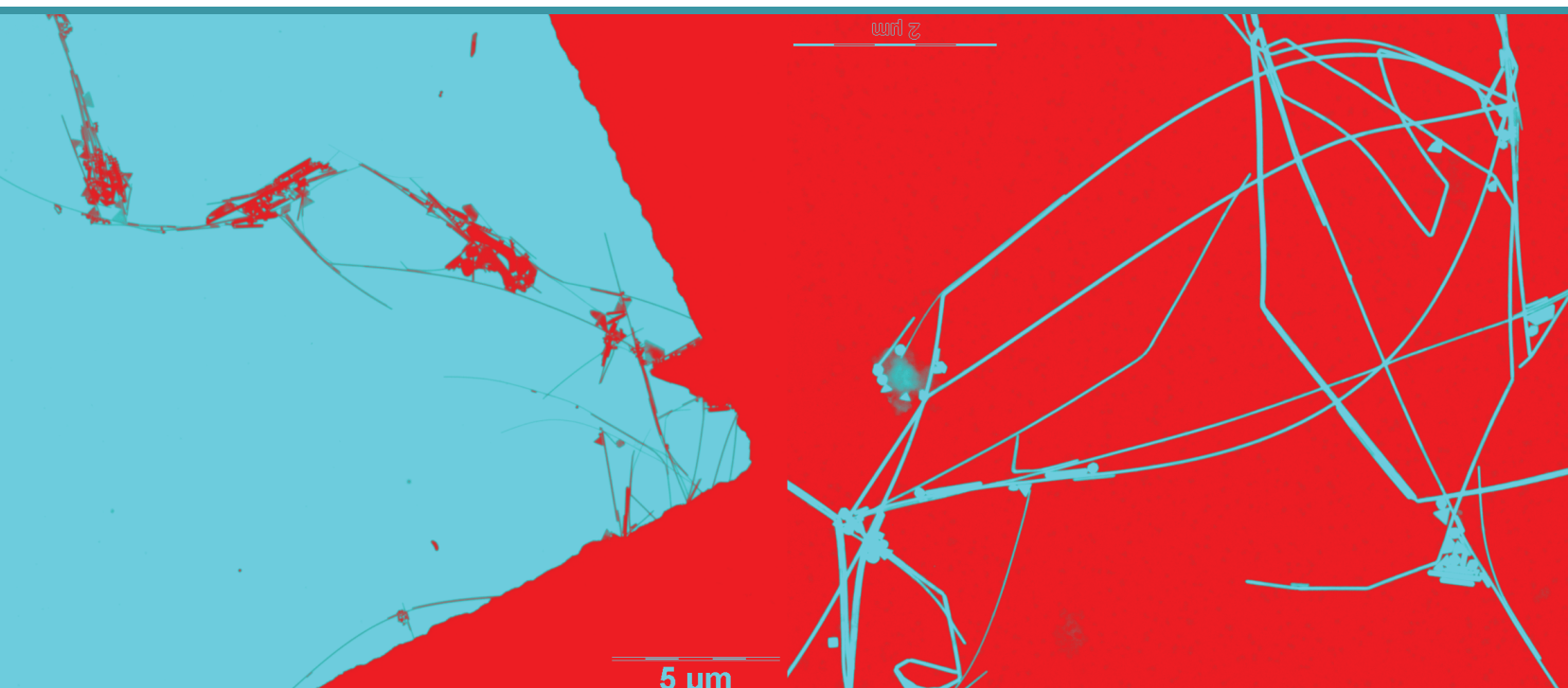
SUMMARY

There are different types of vehicles, basically organic-polymeric and inorganic. Organic can be divided into capsules and sponges, including liposomes or PLGA, while inorganic can be solid or hollow NPs. A successful case is the use of albumin aggregates as NPs, which trap paclitaxel to treat breast cancer, while other peptides and biological nanoparticles are also being explored. The latter should represent the most biocompatible NPs. Among the most commonly used inorganic materials are gold and iron oxide, while other materials (SiO₂, H₂O, TiO₂), hollow NPs of 3D transition or noble metals are being developed in the research laboratories at present. Also, some drugs are made in the NP form, meaning that their aggregated form is the vehicle and the released form the active principle.

There are different types of drugs. In principle, if one is innovating with the vehicle, it is closer to the clinics wish to use a very well-known drug, down to the phenotypic response to it, rather than use a new drug with a new carrier. Therefore, the most carried drugs have been taxanes and platinum derivatives. However, the majority of the most promising drugs fail in Phase III clinical trials due to high toxicity; therefore, in order to value all of the effort made to develop new drugs that have failed in phase III, encapsulating and directing them is a very powerful strategy.

There are different types of targets. Due to the inherent nature of carriers, the targets for nano-oncology have been either where NPs accumulate, such as in the liver or the immune system, as hepatic cancer and leukaemia, or the most prevalent ones, such as the colon and lung. Prostate and ovarian tumours, which are places that are prone to the passive accumulation of carriers, have also been the subject of research. Finally, brain tumours, due to the difficulty in treatment, severity of the disease, difficulty to perform surgery and the absence of metastasis, have also been the target of nanomedicine, supported by the fact that the presence of a tumour in the brain often disrupts the blood brain barrier, allowing NPs to reach the CNS.

There are a number of open challenges. On the one hand, the design of the vehicle has to be improved to precisely control where it goes and in what state it reaches its target to exploit the potential for passive accumulation. The EPR effect is not yet fully described and the limits are also not understood; this should take advantage of the particular vascularity of tumours. The changes in pharmacokinetics have led us to completely re-consider the way in which we dose the drugs. In fact, the full ADME (administration distribution metabolism/degradation expulsion) of the nanocarriers, both with and without loaded drugs, needs to be determined. Once the perfect vehicle has been designed, the next challenge will be to produce it industrially with high quality (monodispersity and reproducibility).



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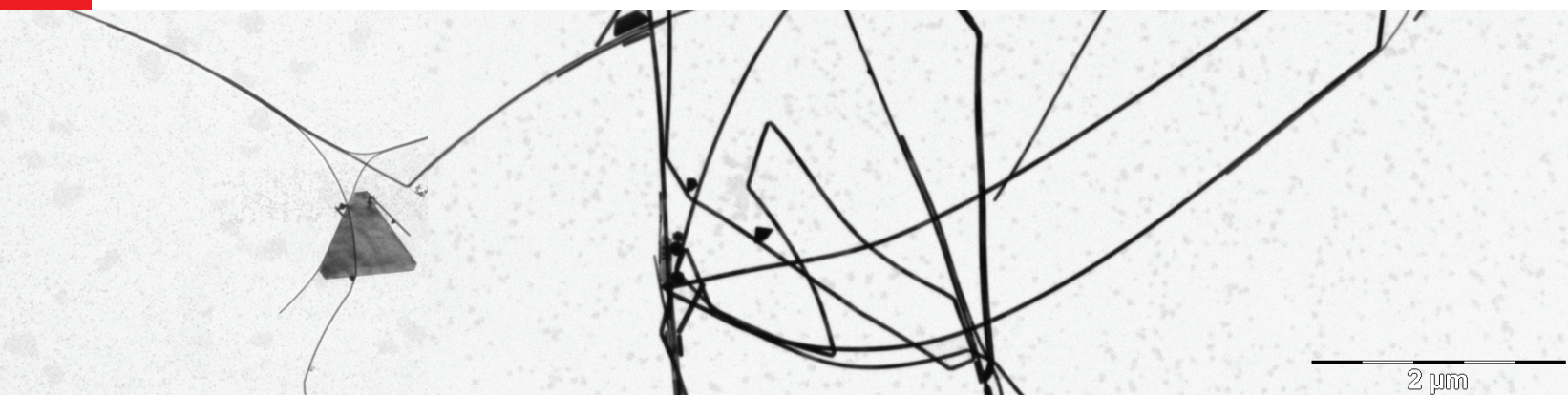
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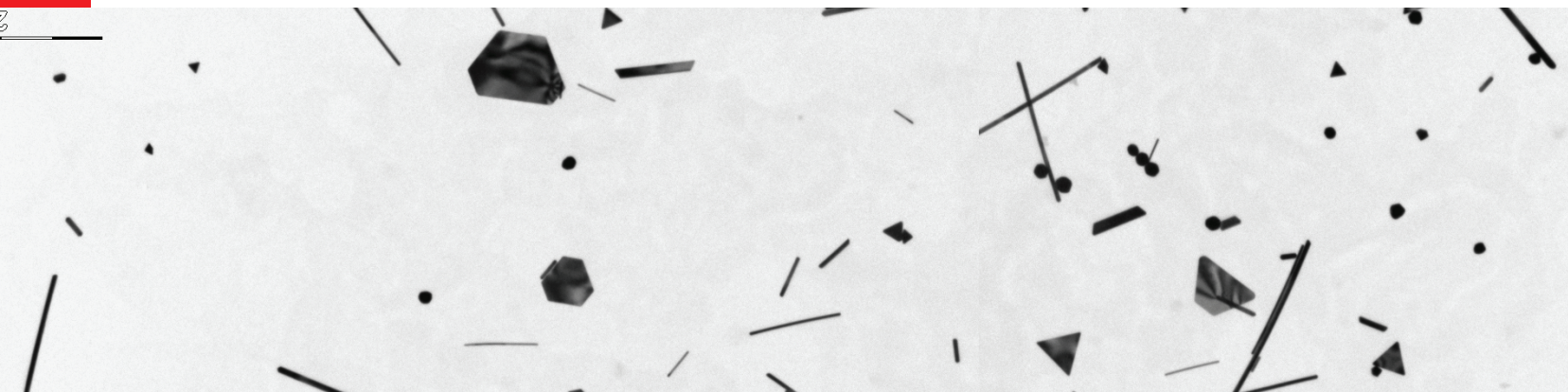
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Nano-Oncology, the Turning Point

PART II State of the Art



NANO-ONCOLOGY, THE TURNING POINT PART II

State of the Art

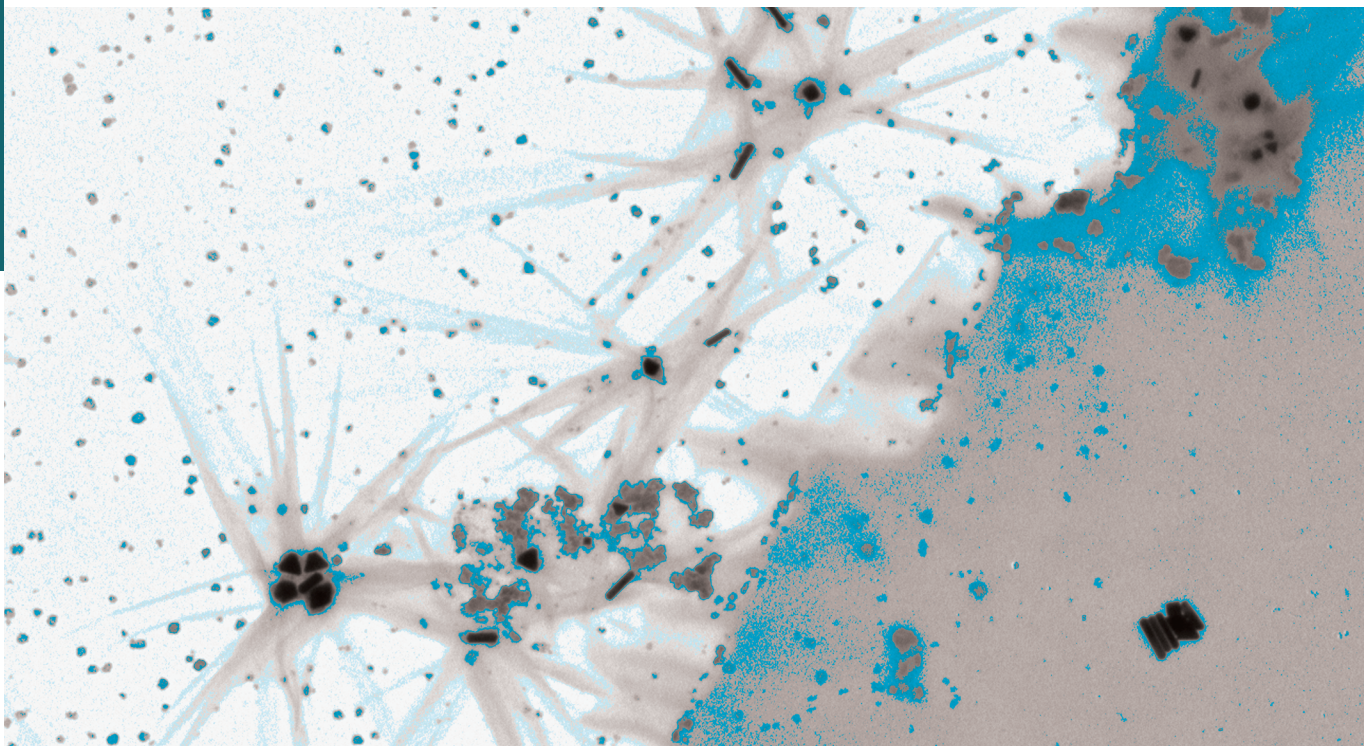
Here we review what efforts are doing nanotechnologists to treat cancer and what challenges scientist have to address in order to permit the final clinical development of nanomedicines, first in oncology and then in the rest of the medical sciences. It is important to note that oncology is the playground for innovative medicine.

In the past 5 years, a large number of advances in the design of nanomedicines to treat cancer has been reported. In fact, the specialized journals have clearly determined that **Nanoparticles Closer and Closer of Cancer Therapy** [1].

"Nanoparticles provide opportunities for designing and tuning properties that are not possible with other types of therapeutics, and as more clinical data become available, the nanoparticle approach should improve further as the optimal properties are elucidated. Nanoparticle-based therapeutics are evolving, and newer, more sophisticated multifunctional nanoparticles are reaching the clinic. Results from these trials are already fuelling enthusiasm for this type of therapeutic modality. Nanoparticles — particles in the size range 1–100 nm — are emerging as

a class of therapeutics for cancer. Early clinical results suggest that nanoparticle therapeutics can show enhanced efficacy, while simultaneously reducing side effects, owing to properties such as more targeted localization in tumours and active cellular uptake. Here, we highlight the features of nanoparticle therapeutics that distinguish them from previous anticancer therapies, and describe how these features provide the potential for therapeutic effects that are not achievable with other modalities. While large number of preclinical studies have been published, the emphasis here is placed on preclinical and clinical studies that are likely to affect clinical investigations and their implications for advancing the treatment of patients with cancer". These are some of them representative of many other.

Diagnosis Circulating Tumoral Cells



It has been said that a tumor is detected when it has 10^7 cells, and that it causes death when it reaches 10^9 cells, this 100 times is the treatment window, therefore, if tumours were detected earlier, the time for therapy will increase in addition of the benefits to treat less developed malignancies. On the other side, the earlier is the stage of disease development, the more difficult is the accurate diagnosis. Therefore, efforts in improving sensing and diagnosis are significant in nanoscience thanks to the exotic properties of nanoparticles and their size similar to biological molecules.

For example designing a **Biosensor to Detect a Single Cancer Marker Protein** [2]. Just months after setting a **record for detecting the smallest single virus in solution** [3], researchers have announced a new breakthrough: They used a nano-enhanced version of their patented microcavity biosensor to detect a single cancer marker protein, which is one-sixth the size of the smallest virus, and even smaller molecules below the mass of all known markers. This achievement shatters the previous

record, setting a new benchmark for the most sensitive limit of detection, and may significantly advance early disease diagnostics. Scientist were able to detect in solution the smallest known RNA virus, MS2, with a mass of 6 attograms. “An attogram is a millionth of a millionth of a millionth of a gram, and we believe that our new limit of detection may be smaller than 0.01 attogram.” In 2012, the researchers set the first sizing record by treating a novel biosensor with plasmonic gold nano-receptors, enhancing the electric field of the sensor and allowing even the smallest shifts in resonant frequency to be detected. Their plan was to design a medical diagnostic device capable of identifying a single virus particle in a point-of-care setting, without the use of special assay preparations. The microcavity is a plasmonic one made out of a gold shell covered with random bumps of roughly the size of a protein. These irregularities generate their own highly reactive local sensitivity field extending out several nanometers, amplifying the capabilities of the sensor far beyond original predictions. “A virus is far too large to be

aided in detection by this field” while “proteins are just a few nanometers across—exactly the right size to register in this space.”

Similarly, we have seen **First Use of Label-Free Nanosensors with Physiological Solutions** [4]. Thanks to the unique physical signatures of nanoparticles, researchers used nanosensors to measure cancer biomarkers in whole blood (a complicated solution containing proteins and ions and other substances that affect detection) for the first time, by using nanowire sensors to detect and measure concentrations of two specific biomarkers: one for prostate cancer and the other for breast cancer. Their findings could dramatically simplify the way physicians test for biomarkers of cancer and other diseases. To overcome the challenge of whole blood detection, researchers developed a novel device that acts as a filter, catching the biomarkers—in this case, antigens specific to prostate and breast cancer—on a chip while washing away the rest of the blood. Creating a buildup of the antigens on the chip allows for detection down to extremely small concentrations, on the order of picograms per milliliter, to within an accuracy of plus or minus 10 percent. This is the equivalent of being able to detect the concentration of a single grain of salt dissolved in a large swimming pool. Current tests are also labor intensive. They involve taking a blood sample, sending it to a lab, using a centrifuge to separate the different components, isolating the plasma and putting it through an hours-long chemical analysis. The whole process takes several days. In comparison, the new device is able to read out biomarker concentrations in just a few minutes. “Doctors could have these small, portable devices in their offices and get nearly instant readings, they could also carry them into the field and test patients on site.”

This is developing new ways of sensing, and in the future, we will not use blood, but liquid excreted from the body, and sweat or tears, and breath (**Diagnosis Through Breath** [5]) with carbon nanotubes or gold. **Lung Cancer Nanobiosensor** [6]. In 2006 researchers established that dogs could detect cancer by sniffing the exhaled breath of

cancer patients. Now, using nanoscale arrays of detectors, researchers have shown that a compact mechanical device also can sniff out lung cancer in humans with a network of chemically modified carbon nanotubes to create a multicomponent sensor capable of discriminating between a healthy breath and one characteristic of lung cancer patients. This was also used to discriminate between the breath of patients with non-small cell lung cancer and chronic obstructive pulmonary disease (COPD) or discriminate between exhaled breath of healthy states and of end-stage renal disease states. Indeed, it has been discovered that an electronic nose developed for air quality monitoring on Space Shuttle Endeavour can also be used to detect odour differences in normal and cancerous brain cells. The results of the pilot study open up new possibilities for neurosurgeons in the fight against brain cancer. The electronic nose, which is to be installed on the International Space Station in order to automatically monitor the station’s air, can detect contaminants within a range of one to approximately 10,000 parts per million. In miniaturization, mimicking the sense of smell has been a major target. The smell is composed of thousands integrated specific receptors, in fact, the smell occupies about a thousand of gens and such a huge analyzing library has to be shrunk to fit in a body.

As with the carbon nanotube arrays, gold nanoparticles are an alternative. “A highly sensitive and fast-response array of sensors based on gold nanoparticles, in combination with pattern recognition methods, can **distinguish** [7] between the odor prints of non-small-cell lung cancer and negative controls with 100% accuracy, with no need for preconcentration techniques. Additionally, preliminary results indicated that the same array of sensors might serve as a better tool for understanding the biochemical source of volatile organic compounds that might occur in cancer cells and appear in the exhaled breath, as compared to traditional spectrometry techniques. The reported results provide a launching pad to initiate a bedside tool that might be able to screen for early stages of lung cancer and allow higher cure rates. In addition, such a tool might be used for the immediate

diagnosis of fresh (frozen) tissues of lung cancer in operating rooms, where a dichotomic diagnosis is crucial to guide surgeons.” “Conventional diagnostic methods for lung cancer are unsuitable for widespread screening because they are expensive and occasionally miss tumours. Gas chromatography/mass spectrometry studies have shown that several volatile organic compounds, which normally appear at levels of 1–20 ppb in healthy human breath, are elevated to levels between 10 and 100 ppb in lung cancer patients.”

Also, screening for potential disease individual susceptibility, taking advantage that **Nanotechnology Is Able To Examine Single Molecules** [8], by nanocantilever approaches, steaming from the scanning probe microscopes, thus determine gene expression, paving the way for scientists to more accurately examine single cancer cells. Previously, researchers have been able to determine gene expression using microarray technology or DNA sequencing. However, such processes could not effectively measure single gene transcripts-the building blocks of gene expression. With their new approach, researchers were able to isolate and identify individual transcript molecules-a sensitivity not achieved with earlier methods.

In general, **Nanoparticle Could Help Detect Many Diseases Early** [9] as in the example of a nanoparticle capable of detecting and imaging trace amounts of hydrogen peroxide in animals, signature of immune response. The nanoparticles, thought to be completely nontoxic, could some day be used as a simple, all-purpose diagnostic tool to detect the earliest stages of any disease that involves chronic inflammation — everything from cancer and Alzheimer’s to heart disease and arthritis. The nanoparticle polymer is made of peroxalate esters. A fluorescent dye (pentacene) is then encapsulated into the polymer. When the nano particles bump into hydrogen peroxide, they excite the dye, which then emits photons (or light) that can be detected. And ideally, **Find Disease Before It Starts** [10]. Nanotechnology would do so by improving the quality of images produced by one of the most common diagnostic tools used in doctors’ offices, the UltraSound machine. In

laboratory experiments on mice, researchers found that nano-sized particles injected into the animals improved the resulting images. This study is one of the first reports showing that ultrasound can detect these tiny particles when they are inside the body. We ultimately want to identify disease at its cellular level, at its very earliest stage.” The hope is that combining ultrasound and nanotechnology may provide a definitive diagnosis in lieu of an invasive procedure like a biopsy.

Other interesting aspect is the observation of the mechanical properties of biological matter at the nanoscale. Thus, **Biomechanical Factor In Malignancies Have Been Identified** [11]. Evidence is mounting that the development and spread of cancer, long attributed to gene expression and chemical signaling gone awry, involves a biomechanical component as well. Now have been observed that a malignant activity of a critical cellular protein system can arise from what essentially are protein traffic jams. Running proteins through an array of gold nanodots, researchers found that transport of a receptor-ligand complex was normal in healthier cell lines but became jammed in diseased cell lines, with the worst jamming taking place in the cells that were the most diseased, concluding that “Our observations suggest the cytoskeleton is the culprit and that drugs modulating the cytoskeleton might also therapeutically modulate EphA2 clustering, thereby reducing pathological behavior.”

Or similarly, as the detection of **The Nanomechanical Signature of Breast Cancer** [12]. The spread of cancer cells from primary tumors to other parts of the body remains the leading cause of cancer-related deaths. Researcher showed how the unique nanomechanical properties of breast cancer cells are fundamental to the process of metastasis. Breast cancer is the most common form of cancer in women. Despite major scientific advancements in our understanding of the disease, breast cancer diagnostics remains slow and subjective. Here, the real danger lies in the lack of knowing whether metastasis, the spread of cancer, has already occurred. Nevertheless, important clues may be hidden in how metastasis

is linked to specific structural alterations in both cancer cells and the surrounding extracellular matrix. To study that, an ultra-sharp atomic force microscope tip of several nanometers in size that is used as a local mechanical probe to “feel” the cells and extracellular structures within a tumor biopsy. In this way, a nanomechanical “fingerprint” of the tissue is obtained by systematically acquiring tens of thousands of force measurements over an entire biopsy. Subsequent analysis of over one hundred patient biopsies could confirm that the fingerprint of malignant breast tumors is markedly different as compared to healthy tissue and benign tumors. Measurements reflect the heterogeneous make-up of malignant tissue whereas healthy tissue and benign tumors are more homogenous. Strikingly, malignant tissue also featured a marked predominance of “soft” regions that is a characteristic of cancer cells and the altered microenvironment at the tumor core. The significance of these findings lies in reconciling the notion that soft cancer cells can more easily deform and “squeeze” through their surroundings. Indeed, the presence of the same type of “soft” phenotype in secondary lung tumors of mice reinforces the close correlation between the physical properties of cancer cells and their metastatic potential. This has the potential to prognose metastasis.

Related to that, **Cancer Metastasis Mechanism Has Been Studied at Nanometer Level** [13]. Researchers have developed an optical system to image with a spatial precision of 10 nanometer in vivo. The optical system enables to visualize protein and drug at single molecular level in tumor-bearing mice which is implanted with human breast cancer cells. The most terrible biological property of cancer is its ability to spread to other organs (metastasis). The research group labeled the metastasis-promoting protein on the cell membrane with fluorescence nanoparticles and has analyzed the protein dynamics with the newly developed optical device. In this study, they firstly discovered following cancer mechanisms using mice: 1. A change of cell morphology is important for cancer metastasis. 2. Cancer cells showed increases in migration speed (diffusion speed) of membrane protein (over 1000-fold) with progression of metastasis. The change of

migration speed is important for activation of cancer metastasis.

This mechanical studies are also contributing to correlate microstructure with class. As, for example, when **Nanosopic Changes to Pancreatic Cells Reveal Cancer** [14]. Researchers have developed a way to examine cell biopsies and detect never-before-seen signs of early-stage pancreatic cancer, what may one day help diagnose cancers of the pancreas and, potentially, other organs at their earliest and most treatable stages, before they spread. Pancreatic cancer is typically diagnosed by hospital pathologists who look for telltale changes to the morphology of pancreatic cells when they examine cell biopsies under the microscope. The problem is that in the early stages of cancer, many early-stage cancer cells appear normal. By the time the cancerous cells undergo observable changes, it may be too late in the disease progression for effective treatment. It works by detecting fluctuations in the cells’ refractive index (an optical property that measures how cells bend light passing through them). These fluctuations are influenced by nanoscopic changes to the cells’ interior architecture. The more architectural disorder there is inside the cell, the more the refractive index fluctuates.

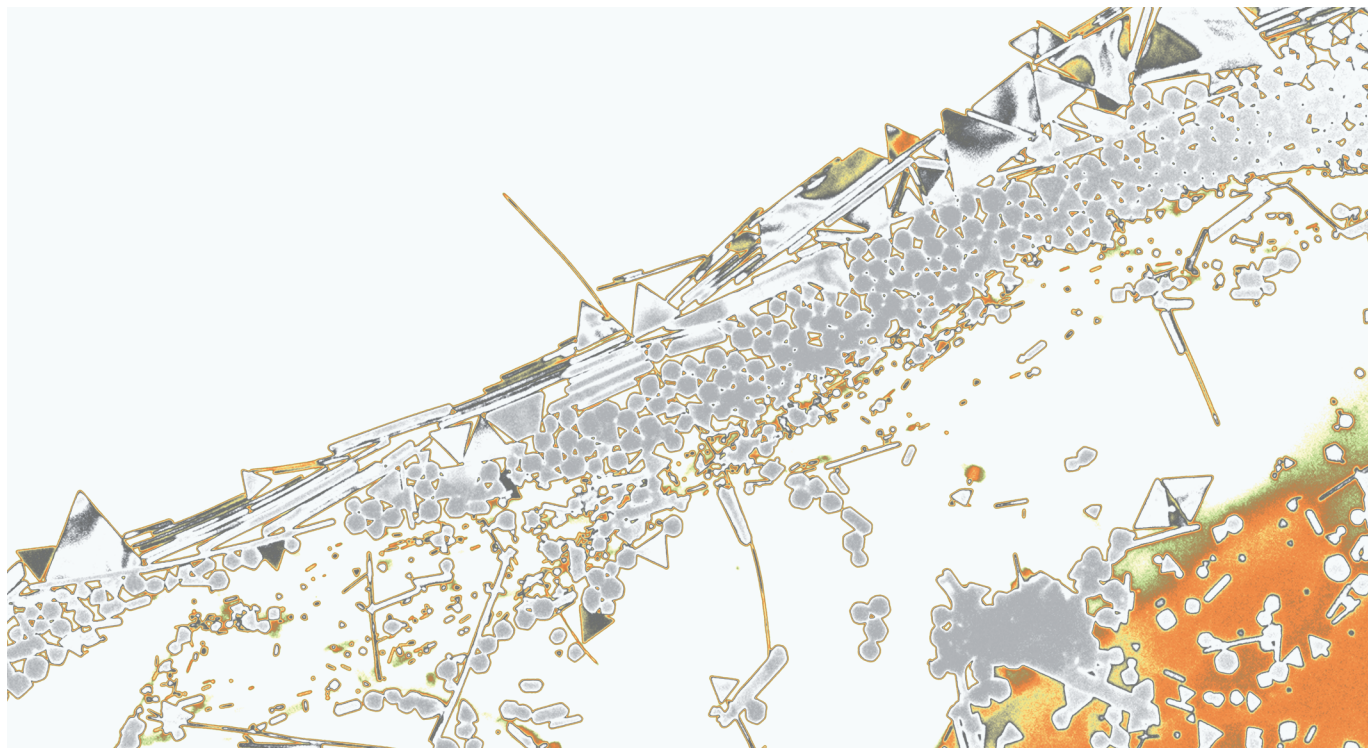
In diagnosis also, the strong absorbance of some gold nanoparticles in the Near Infrared regime has allowed **Gold Nanorods Image Tumors** [15]. A growing body of research has demonstrated that gold nanorods can serve as extremely bright imaging agents. Now, by linking gold nanorods to an antibody that binds to tumor cells, researchers have found that gold nanorods will align themselves in an ordered fashion on the surface of cancer cells, further intensifying the optical signal the nanorods produce and providing a unique optical signature for tumor cells.

We are already seeing how more complex multifunctional materials are constantly being developed, as in the case of a **New Type of Nanoparticles** [16]. Researchers have developed a type of nanoparticles that could be used in tests for environmental pollution or contamination of

food products, and for medical diagnostics. The particles, about 100 to 200 nanometers in size, are luminescent, magnetic and inexpensive to make, and can be tagged with antibodies. They are made up of a magnetic core of iron oxide or iron/neodymium/cobalt oxide coated in a shell of europium and gadolinium oxide. When stimulated with a laser, europium emits red light at a very specific wavelength. The nanoparticles can be manipulated with magnets and detected by fluorescence. They could also be labeled with other fluorescent labels in different colors, or used as part of an assay with other fluorescent labels. The built-in europium luminescence acts as an internal standard, making it easier to carry out accurate quantitative assays.

And we have also seen the **Emergence of Femtomedicine** [17]. Bombarding DNA nucleotides and mammalian meat with ‘femto-neutrons’ has opened up the path to femtomedicine, an entirely new cancer diagnostics. Femto-neutrons or ‘femtons’ are fast neutrons of femto-meter wave-length, a million times shorter than the current nanotechnology medical diagnostic probes that operate on nanometer scale. Researchers were able to detect oxygen differences as tiny as 1 atom of oxygen per molecule, one foot away, it is claimed. Since ‘hypoxic’ cancerous tumors contain 50% to 90% less oxygen than healthy tissue, if you find an oxygen difference between a tumor and the adjacent healthy tissue – you have diagnosed cancer! This aims to allow to provide needleless biopsy with negligible ‘false negatives’ that is a quantum leap over the current technologies. It should facilitate an early warning, walk-in, painless, instant cancer diagnosis from outside the body, without intravenous fluid”. It will be used in tandem with any one of the imaging systems that have achieved very high sensitivity, almost 98%, in detecting tumors; but have a low ‘specificity’, about 70%, in differentiating healthy from malignant ones, thus missing an unacceptably large number of malignancies. This will be accomplished by making patients inhale ‘carbogen’, an oxygen enriched gas.

Drug Delivery



For many reasons, drug delivery is a field where NPs are expected to have a significant impact (in treatment, and consequently, understanding of disease). Recently, we have seen several *First-Time* news as: **First-in-Man Trial of RNAi Therapeutics Delivered with Lipid Nanoparticles** [18]. For the first time that the therapeutic effect of RNAi (RNA interference) has been demonstrated in humans. Harnessing RNAi to silence genes involved in the development and growth of cancer cells is an important step forward in developing a new and more targeted type of cancer therapy. “This is the first evidence to show that RNAi can be administered to cancer patients effectively, leading to significant tumour response.” Researchers have developed a lipid nanoparticle approach that can deliver two of the RNAi molecules targeted against the genes encoding two key proteins involved in the development of cancer cells (VEGF and KSP). This system takes the form of a novel drug made up of RNAi molecules and lipid nanoparticles. **RNAi** [19] is a revolution in biology,

representing a breakthrough in understanding how genes are turned on and off in cells, and a completely new approach to drug discovery and development. RNAi is a natural process of gene silencing that occurs in organisms ranging from plants to mammals. By harnessing the natural biological process of RNAi occurring in our cells, the creation of a major new class of medicines, known as RNAi therapeutics, is on the horizon. Also, **First Drug-Carrying Nanoparticles that Look and Act like Cells** [20], by cloaking nanoparticles in the membranes of white blood cells, researchers may have found a way to prevent the body from recognizing and destroying them before they deliver their drug payloads. “The goal was to make a particle that is camouflaged within our bodies and escapes the surveillance of the immune system to reach its target undiscovered”. This is accomplished with lipids and proteins present on the membrane of the very same cells of the immune system. Researchers transferred the cell membranes to the surfaces of the particles and the result is that the body now recognizes these particles as its own and

does not readily remove them.

Nanoparticles can deliver different types of drugs to specific cell types, for example, chemotherapy to cancer cells. But for all the benefits they offer and to get to where they need to go and deliver the needed drug, nanoparticles must somehow evade the body's immune system that recognizes them as intruders. The ability of the body's defenses to destroy nanoparticles is a major barrier to the use of nanotechnology in medicine. Systemically administered nanoparticles are captured and removed from the body within few minutes. With the membrane coating, they can survive for hours unharmed. A strategy prevents the binding of opsonins —signaling proteins that activate the immune system. Similarly, **First Targeted and Programmable Nanomedicine to Show Clinical Anti-Tumor Effects** [21]. Targeted and programmable therapeutics are capable of up to a ten-fold increase in drug concentration at tumor sites, which lead to substantially better efficacy and safety. A PLGA carrier has the ability to concentrate in tumors and provide preclinical and clinical data demonstrating efficacy, safety and pharmacological properties that are superior to and highly differentiated from the parent chemotherapeutic drug, docetaxel. This is the first clinical-stage targeted therapeutic nanoparticle with programmable pharmacological properties, including particle circulation time, pharmacokinetic profile, biodistribution and release profile. "Previous attempts to develop targeted nanoparticles have not translated into clinical success because of the inherent difficulty of designing and scaling up a particle capable of targeting, long-circulation via immune-response evasion, and controlled drug release". Besides, the **World's First Nanoparticle-Based Cancer Treatment to Come to Market** [22], was reported on 2010. Approval was granted for the treatment of brain tumors. This novel therapy involves the instillation directly into the tumor of a fluid containing special iron oxide nanoparticles. These magnetic nanoparticles are then subjected to a controlled magnetic field so that they oscillate and generate heat. The elevated temperature within the tumor causes the cancer

cells to be damaged or destroyed. The regulatory approval was received based on the results of a clinical study in patients suffering from recurrent glioblastoma, a particularly aggressive and deadly form of brain tumor. And it was granted not just for glioblastoma but for the treatment of all brain tumors.. In these clinical trials, the new therapy was able to demonstrate its remarkable effectiveness, with median patient survival time increased from 6.2 months using conventional therapies to 13.4 months using nanotherapy in combination with radiotherapy. Median patient survival following diagnosis of the recurrence was thus more than doubled. Furthermore, compared to existing conventional treatments, the side effects and patient discomfort associated with the new therapy are minimal.

Also, using nanotechnology, scientists have developed a **Localized and Controlled Drug Delivery** [23] method that is invisible to the immune system, a discovery that could provide newer and more effective treatments for cancer and other diseases. The study provides an example of the enormous potential and clinical significance that nanomaterials may represent in such fields as oncology, endocrinology and cardiology. The researchers used nanoscale polymer films, about four nanometers per layer, to build a sort of matrix or platform to hold and slowly release an anti-inflammatory drug. The nanomaterial technology serves as a non-invasive and biocompatible platform for the delivery of a broad range of therapeutics. The technology also may prove to be an effective approach for delivering multiple drugs, controlling the sequence of multi-drug delivery strategies and enhancing the life spans of commonly implanted devices such as cardiac stents, pacemakers and continuous glucose monitors. "For chemotherapy, this system could enhance treatment efficacy while preventing uncontrolled delivery and the resultant patient side effects."

Another example of drug delivery is the **Enhancement of In Vivo Anticancer Effects of Cisplatin** [24]. Another set of experiments that show the promise of nanoparticles and carbon

nanostructures as efficient vehicles for cancer treatment. Cisplatin was incorporated inside single-wall carbon nanohorns with holes opened by a nanoprecipitation method that involved dispersion of cisplatin and the nanostructures in a solvent followed by the solvent evaporation. The incorporated cisplatin increased from the previously reported value of 15 to 46%, and the total release of cisplatin also increased from 60 to 100% by changing the solvent from dimethylformamide to water. Concurrently, in vitro anticancer efficiency increased to 46 times greater than that of the free cisplatin. In vivo, cisplatin vehiculized by the carbon nanohorn intratumorally injected to transplanted tumors of mice suppressed the tumor growth more than the intact cisplatin. Adhesion of the nanostructure to the cell surfaces in vitro and within the tumor tissues in vivo is probably the key in the observed effects. However, the carbon nanohorns show also cytotoxicity, what may on one side increase the toxicity of the conjugated drug but also result in undesired toxic side effects due to the inherent toxicity of poorly hydrophilic or very large carbon nanotubes, fullerenes and their derivatives.

Similar results were observed with carbon nanotubes: **Cisplatin and Carbon Nanotubes** [25]. Antineoplastic effects of cisplatin [26], a paradigm of serendipity, were discovered when applying electric fields to *C. Elegans*. In that case, the Pt(II) cations released from the electrodes interfered with cellular duplication and the *C. Elegans* growth to gigantic sizes. First, it was thought that the applied electrical field induced organism growth. However, later on, it was found that cisplatin [27] irreversibly attaches to the N residues of the DNA impeding cell reproduction. Since then, it has been one of the most used antitumoral drugs and still today is widely used in the treatment of the most prevalent tumours. In addition, cisplatin [28] derivatives as carboplatin or oxiplatin have shown also beneficial therapeutic effects, indicating that modifications of cisplatin may be of medical interest. Therefore many compounds based on Pt(II) have been produced showing biological activity. However, few of them have shown medical relevance yet. The loss of activity in the body can be associated with deactivation

of the Pt(II) cation by sulfure containing molecules (cisteines) or by a unproper biodistribution of the drug, among others. In a recent work, to overcome these complications, platinum (IV) compounds have been conjugated to carbon nanotubes. The carbon nanotubes should act then as Longboat Delivery Systems for Platinum (IV). Such nanocomposites are internalized by endocytosis into a endosome where its low pH reduces Platinum (IV) to Platinum (II) delivering a large amount of cisplatin(II) to the cell, increasing efficiently its killing effects. In addition, circulating Platinum (IV) compounds are non toxic (it is the valence II compound the toxic one). Now it has to be observed the compound biodistribution and side effects since generally platinum chemotherapies are interrupted due to size effects of nefro toxicity or renal toxicity.

Researchers' Nanotube Findings Give Boost to Potential Biomedical Applications [29]. A team of scientists has tracked the movement of carbon nanotubes through the digestive systems of mice. They have determined that the nanotubes do not exhibit any toxicity in the mice, and are safely expelled after delivering their payload. (See related posts: **First Direct Images of Carbon Nanotubes Entering Cells** [30] and **Nanotube-Producing Bacteria** [31]). As a result, the study paves the way toward future applications of nanotubes in the treatment of illnesses. Previous research by the same team demonstrated that nanotubes can be used to fight cancer. The nanotubes do this in two ways. One method involves shining laser light on the nanotubes, which generates heat to destroy cancer cells. Another method involves attaching medicine to the nanotubes, which are able to accurately 'find' cancerous cells without impacting healthy cells.

Other ways to deliver cisplatin with directed NP was reported using aptamer functionalized Pt(IV) prodrug-PLGA-PEG nanoparticles to deliver the antineoplastic agent to prostate cancer cells. And nanotubes are also promising in different ways as: **Nanotubes That Help Advance Brain Tumor Research** [32]. The potential of carbon nanotubes to diagnose and treat brain tumors may help revolutionize medicine in the

future with its promise to play a role in selective cancer therapy. Researchers hope to boost the brain's own immune response against tumors by delivering cancer-fighting agents via nanotubes. If nanotube technology can be effectively applied to brain tumors, it might also be used to treat stroke, trauma, neurodegenerative disorders and other disease processes in the brain. The nanotubes, which these researchers used on mice, were non toxic in brain cells, did not change cell reproduction and were capable of carrying DNA and siRNA, two types of molecules that encode genetic information. Carbon nanotubes are extremely strong, flexible, heat-resistant, and have very sharp tips.

Gold is also a promising material to, at the nanoscale, carry drugs: **Gold Nanoparticles: a Potential Platform for Target-Specific Therapies in Cancer** [33]. Gold Nanoparticles were strongly supported as a drug-payload delivery system during **2008 NSTI meeting** [34] celebrated in Boston. Dr. Piotr Grodzinski is Director of Nanotechnology for Cancer programs at **Nanotechnology Alliance of National Cancer Institute (NCI)** [35] in Bethesda, Maryland. In his keynote lecture "Clinical translation of Nanotechnology for Cancer: The NCI Alliance's Perspective", he reviewed the most relevant NCI current initiatives and Gold Nanoparticles applications were introduced as a major area of focus: a recombinant human tumor necrosis factor alpha (a known tumor-killing agent) bound to the surface of Gold Nanoparticles (Phase I) and AuroLase Cancer Therapy, a novel cancer treatment that combines the unique physical and optical properties of Gold Nanoparticles with a near infrared laser source to thermally destroy cancer cells without significant damage to surrounding tissue. The NCI, part of the National Institutes of Health, is engaged in efforts to harness the power of nanotechnology to radically change the way we diagnose, treat and prevent cancer.

And of course, **cisplatin delivered by gold** [36] with a pH controlled released has shown how the therapeutic benefits of cisplatin are improved while the side effects radically diminished opening the way to a more intense treatment to fight to resistant

tumors while keeping the patient in good conditions. Here the use of gold nanoparticles (AuNPs) to detoxify the antitumoral agent cisplatin, linked to a nanoparticle via a pH-sensitive coordination bond for endosomal release, was presented. The NP conjugate design has very important effects on pharmacokinetics, conjugate evolution and biodistribution, and results in an absence of observed toxicity. Besides, AuNPs present unique opportunities as drug delivery scaffolds due to their size and surface tunability. Here researchers showed that cisplatin-induced toxicity is clearly reduced without affecting the therapeutic benefits in mice models. The NPs not only act as carriers, but also protect the drug from deactivation by plasma proteins until conjugates are internalized in cells and cisplatin is released. Additionally, the possibility to track the drug (Pt) and vehicle (Au) separately as a function of organ and time enables a better understanding of how nanocarriers are processed by the organism.

But as commented, the most elegant way of delivering drugs is when the **Drug Delivers Itself** [37]. This is when the drug can be administrated in the form of a nanoparticle that yields controlledly its components while disintegrating. The problem of efficiently delivering drugs, especially those that are hydrophobic or water-repellant, to tumors or other disease sites has long challenged scientists to develop innovative delivery systems that keep these drugs intact until reaching their targets. Now scientists have developed an innovative solution in which the delivery system is the drug itself. They describe for the first time in Molecular Pharmaceutics a drug delivery system that consists of nanocrystals of a hydrophobic drug.

Another innovative vehicle is to use natural biological capsules as **Cage Nanoparticles to Treat Cancer** [38]. Researchers have used an engineered form of ferritin, a cage-like iron storage protein, to both synthesize and deliver iron oxide nanoparticles to tumors for imaging and hyperthermia. The researchers note that the use of other cage-like proteins, instead of ferritin, could provide a wide range of tools for targeting tumors and delivering imaging agents and drugs to

malignant cells.

The abilities of NPs to reach the cytosol by crossing the cell membrane, or escaping from the endosome in which they are internalized (only ions and small molecules has the ability to cross the cell membrane) has been also a focus of research. If the different architecture of the cell in tumoral and healthy cells allows to selectively cross the membrane, the effect of the cargo can be more effective. **‘Passkey’ into Cancer** [39]. Scientists developed passkeys that contain a molecule called Bucky amino acid based on pheylalanine, one of the 20 essential amino acids that are strung together like beads on a necklace to build all proteins. Several different Baa-containing peptides, or slivers of protein containing about a dozen amino acids were prepared. In their natural form, with pheylalanine as a link in their chain, these peptides did not pass through the cell walls. Baa-containing peptides could mimick viral proteins and pass through the walls of cancer cells. The peptides were found effective at penetrating the defences of both liver cancer cells and neuroblastoma cells.

Accessing the brain is always difficult. True is that in the case of a malignancy, the tumor itself or due to concomitant surgery, it is disrupted. In any case, the NP can be designed to cross tight cellular junctions. **Nano Drug Crosses Blood-Brain Tumor Barrier** [40]. An experimental drug in early development for aggressive brain tumors can cross the blood-brain tumor barrier, kill tumor cells and block the growth of tumor blood vessels. The laboratory and animal study also showed how the agent targets tumor cells and blood vessels. The findings support further development of the drug as a novel treatment for brain tumors. Glioblastoma multiforme is the most common and aggressive form of brain cancer, with a median survival of about 15 months. A major obstacle to improving treatment is the blood-brain barrier, the name given to the tight fit of cells that make up the blood vessels in the brain. That barrier protects the brain from toxins in the blood but also keeps drugs in the bloodstream from reaching brain tumors. Few drugs have the capacity to cross the tumor blood-brain barrier and specifically target tumor cells. The

vehicle is a nanovesicle drug that has shown activity in glioblastoma, pancreatic cancer and other solid tumors in preclinical studies. The nanovesicles fuse with tumor cells, causing them to self-destruct by apoptosis.

Nanoparticles ‘pH phoresis’ Could Improve Cancer Drug Delivery [41]. Researchers have developed a concept to potentially improve delivery of drugs for cancer treatment using nanoparticles that concentrate and expand in the presence of higher acidity found in tumor cells. The concept involves using nanoparticles made of “weak polybases,” compounds that expand when transported into environments mimicking tumor cells, which have a higher acidity than surrounding tissues. This phenomenon, may provide a useful mechanism for improving the delivery of drugs to cancer cells in solid tumor tissues. Solutions with a pH less than 7 are said to be acidic, and those with a higher pH are basic or alkaline. The pH-foresis concept hinges on using synthetic “polymer micelles,” tiny drug-delivery spheres that harbor medications in their inner core and contain an outer shell made of a material that has been shown to expand dramatically as the pH changes from alkaline to acidic. A twofold size increase could result in a similar increase in the efficiency of drug delivery to tumors.

‘Nanotrain’ for Targeted Cancer Drug Transport [42]. Researchers have developed a “DNA nanotrain” that fast-tracks its payload of cancer-fighting drugs and bioimaging agents to tumor cells deep within the body. The nanotrain’s ability to cost-effectively deliver high doses of drugs to precisely targeted cancers and other medical maladies without leaving behind toxic nano-clutter has been the elusive Holy Grail for scientists studying the teeny-tiny world of DNA nanotechnology. DNA nanotechnology holds great promise as a new way to deliver chemotherapy directly to cancer cells, but until now, researchers have not been able to direct nanotherapies to consistently differentiate cancer cells from healthy ones. Other limiting factors include high costs, too-small amounts of drugs delivered and potential toxic side effects. Compared to existing nanostructures,

a nanotrain could be easier and cheaper to make, is highly specific to cancer cells, has a lot of drug-loading power and it is very much biocompatible.” The DNA nanotrain is a three-dimensional structure composed of short strands of DNA tethered together into one long train. On the end of the nanotrain is an aptamer, a tiny piece of nucleic acid serving as the train’s “locomotive” on biochemical autopilot to home in on and bind to specific cancer cells. Trailing behind are tethered DNA structures that serve as side-by-side, high-capacity “box cars,” transporting bioimaging agents or drug cargos to their targets. The beauty of the nanotrain is that by using different disease biomarkers you can hitch different types of DNA probes as the train’s ‘locomotive’ to recognize and target different types of cancers. And because the DNA probes are so precise in targeting only specific types of cancer cells we’ve seen dramatic reduction in drug toxicity in comparison to standard chemotherapies, which don’t discriminate well between cancerous and healthy cells. DNA nanotrains can be cost-effectively made by mixing bits of DNA in a liquid medium. The mixture is then exposed to a compound that stimulates the pieces of DNA to seek each other out and self-assemble into the DNA nanotrains. The type of cancer cell the DNA nanotrain will seek out and destroy is determined by the specific compound added to the mixture as the trigger. The study demonstrated in vitro and in mice that the DNA nanotrains exclusively target the cancer cells for which their probes were programmed. Once inside, the drug payloads disperse, killing the cancer cells. The biodegradable components of the DNA nanotrains decay with the dead cancer cells and are removed by the body’s normal housekeeping mechanisms. When loaded with anticancer drugs, these nanotrains inhibited tumor growth in mice more than in those that received drugs injected freely into the bloodstream. What’s more exciting is that the mice treated with these nanotrains suffered dramatically fewer side effects than those treated with free drugs. In addition to longer survival and inhibited tumor growth, the mice that were treated with nanotrain drug delivery experienced less weight loss and are in better condition physically than both the mice that received injected therapy and the mouse

control group that received no treatment.

The penetration and potential future of nanooncology can be appreciated in the recent significant secondary school nano-antitumoral projects and proposals. For example, the well known case of Jack Pancrăs or the **17-Year-Old Who Wins 100k \$ for Creating Cancer-Killing Nanoparticle** [43]. *Design of Image-guided, Photo-thermal Controlled Drug Releasing Multifunctional Nanosystem for the Treatment of Cancer Stem Cells*. Cancer stem cells (CSCs) are responsible for initiating and driving tumor growth yet are often resistant to current cancer therapies. In her research, Angela Zhang aimed to design a CSC-targeted, gold and iron oxide-based nanoparticle with a potential to eradicate these cells through a controlled delivery of the drug salinomycin to the site of the tumor. “*I was surprised by the survival rate of patients who had undergone current cancer therapy.*” The multifunctional nanoparticle combines therapy and imaging into a single platform, with the gold and iron-oxide components allowing for both MRI and Photoacoustic imaging. This nanosystem could potentially help overcome cancer resistance, minimize undesirable side effects, and allow for real-time monitoring of treatment efficacy.

All this lead us to developing more and more smarter systems, as when **Nanoparticles Communicate With Each Other Inside the Body to Target Tumors** [44]. Researchers have designed a new type of delivery system in which a first wave of nanoparticles homes in on the tumor, then calls in a much larger second wave that dispenses the cancer drug. This communication between nanoparticles, enabled by the body’s own biochemistry, boosted drug delivery to tumors by more than 40-fold in a mouse study. This new strategy could enhance the effectiveness of many drugs for cancer and other diseases. “What we’ve demonstrated is that nanoparticles can be engineered to do things like communicate with each other in the body, and that these capabilities can improve the efficiency with which they find and treat diseases like cancer”. Scientists drew their inspiration from complex biological systems in which many components work together to achieve

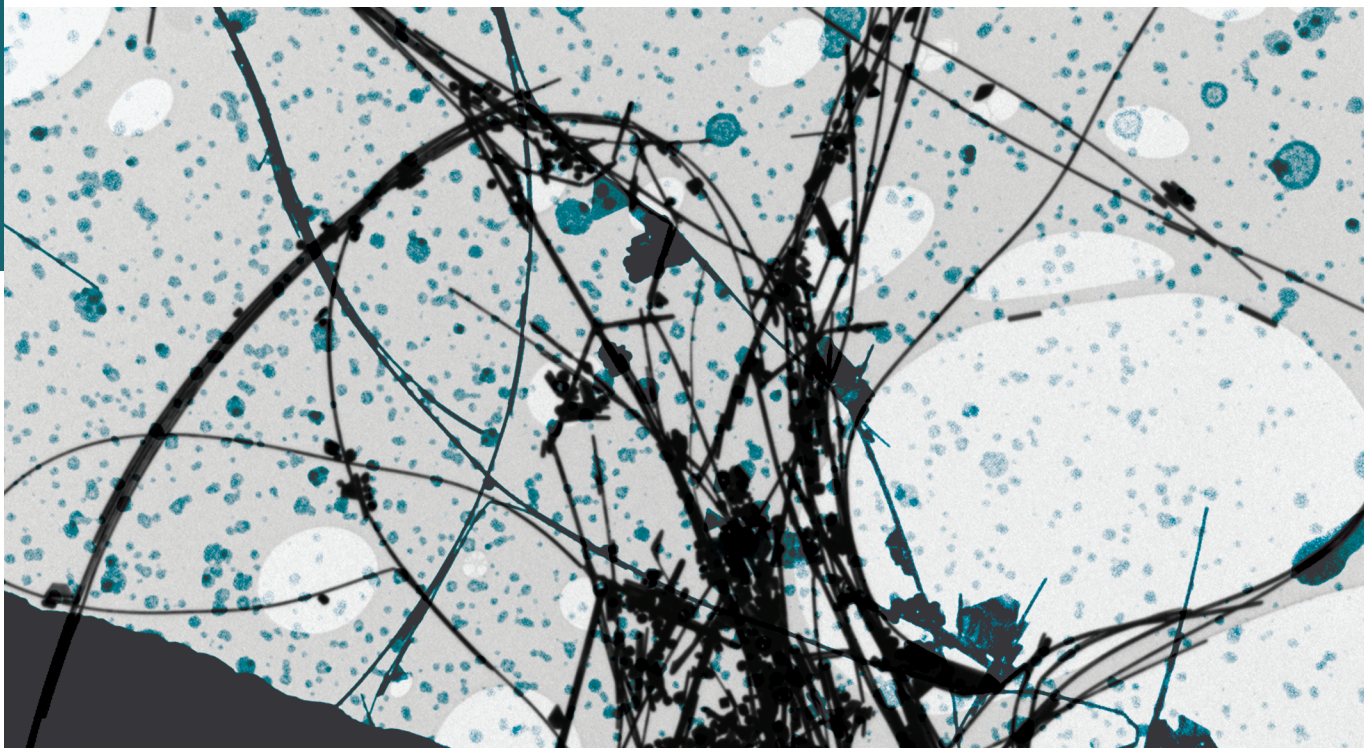
a common goal. For example, the immune system works through highly orchestrated cooperation between many different types of cells. “There are beautiful examples throughout biology where at a system scale, complex behaviors emerge as a result of interaction, cooperation and communication between simple individual components”. Like swarming insects drawing crowds to a food source, a system of nanoparticles and engineered proteins can communicate with one another to raise the concentration of systemically administered drugs at the site of a tumor, a team of scientists has demonstrated. The system harnesses one of the body’s own communication pathways, one that coagulates blood, to accumulate drugs right where they are needed. “We engineered a set of nanoparticles that trigger the body to grow blood clots around tumors. A second set of nanoparticles that recognizes the blood clots then delivers a dose of anti-cancer drug to the tumor”. In a related experiment, researchers designed a [Two-wave nanotherapy: Two-Step Method for Potential Pancreatic Cancer Treatment Proven](#) [45], uses two different kinds of nanoparticles injected into the vein of the patient, one after the other in waves. The first wave of nanoparticles carries a substance that “opens the gate” to access the pancreas cancer cells and the second wave carries the chemotherapy drug that kills the cancer cells.

During this time, the map, the energetics of nanoparticles inside the body, is being revealed which could help to uncover and/or design better routes for efficient delivery of therapeutic cargos. **Scientists Chronicle Nanoparticles’ Journey From the Lungs Into the Body** [46]. Using a novel, real-time imaging system, scientists have tracked a group of near-infrared fluorescent nanoparticles from the airspaces of the lungs, into the body and out again, providing a description of the characteristics and behavior of these minute particles which could be used in developing therapeutic agents to treat pulmonary disease, as well as offering a greater understanding of the health effects of air pollution. The aim of this study was to determine the characteristics and parameters of inhaled nanoparticles that mediate their uptake into the body - from the external

environment, across the alveolar lung surface and into the lymphatic system and blood stream and eventually to other organs. To do this, the scientists made use of the [FLARE™ \(Fluorescence-Assisted Resection and Exploration](#) [47]) imaging system, systematically varying the chemical composition, size, shape and surface charge of a group of near-infrared fluorescent nanoparticles to compare the physiochemical properties of the various engineered particles. The investigators then tracked the movement of the varying nanoparticles in the lungs of rat models over a period of one hour, and also verified results using conventional radioactive tracers. “This study complements our earlier work in which we defined the characteristics of nanoparticles that regulate efficient clearance from the body. With these new findings, which define the characteristics that regulate uptake into the body, we’ve now described a complete ‘cycle’ of nanoparticle trafficking - from the environment, through the lungs, into the body, then out of the kidneys in urine and back to the environment”. Of course this is only for smaller than 6 nm NPs, non immunogenic, not interacting with proteins, that do not aggregate.

It may also happen that the NP response depends on the health status of the body. For example, CeO₂ nanoparticles have been observed to be anti-inflammatory in the case of inflammation, neutral in healthy tissue and toxic in conditions of hypoxia and necrosis as in large tumors, as if it was an intelligent device, or as the observed **Preferential Killing of Cancer Cells Using ZnO Nanoparticles** [48].

Radio Therapy



NP-assisted radiotherapy is also a very promising field, where therapeutic effects were better than even expected, specially in the case of gold, probably by taking advantage of its catalytic properties in addition to its high atomic cross-section to absorb high energy photons of heavy atoms. Other promising approach was a **Breakthrough Cancer-Killing Treatment Has No Side-Effects** [49]. Researchers have developed a new form of radiation therapy that successfully put cancer into remission in mice. This innovative treatment produced none of the harmful side-effects of conventional chemo and radiation cancer therapies. "Since the 1930s, scientists have sought success with a cancer treatment known as boron neutron capture therapy (BNCT [50])," Researchers found the way to make BNCT work by taking advantage of a cancer cell's biology with nanochemistry." Cancer cells grow faster than the majority of normal cells and in the process absorb more materials than normal cells. When those boron-infused cancer cells were exposed to neutrons, a subatomic particle, the boron atom

shattered and selectively tore apart the cancer cells, sparing neighboring healthy cells. A particular form of boron will split when it captures a neutron and release lithium, helium and energy. Like pool balls careening around a billiards table, the helium and lithium atoms penetrate the cancer cell and destroy it from the inside without harming the surrounding tissues.

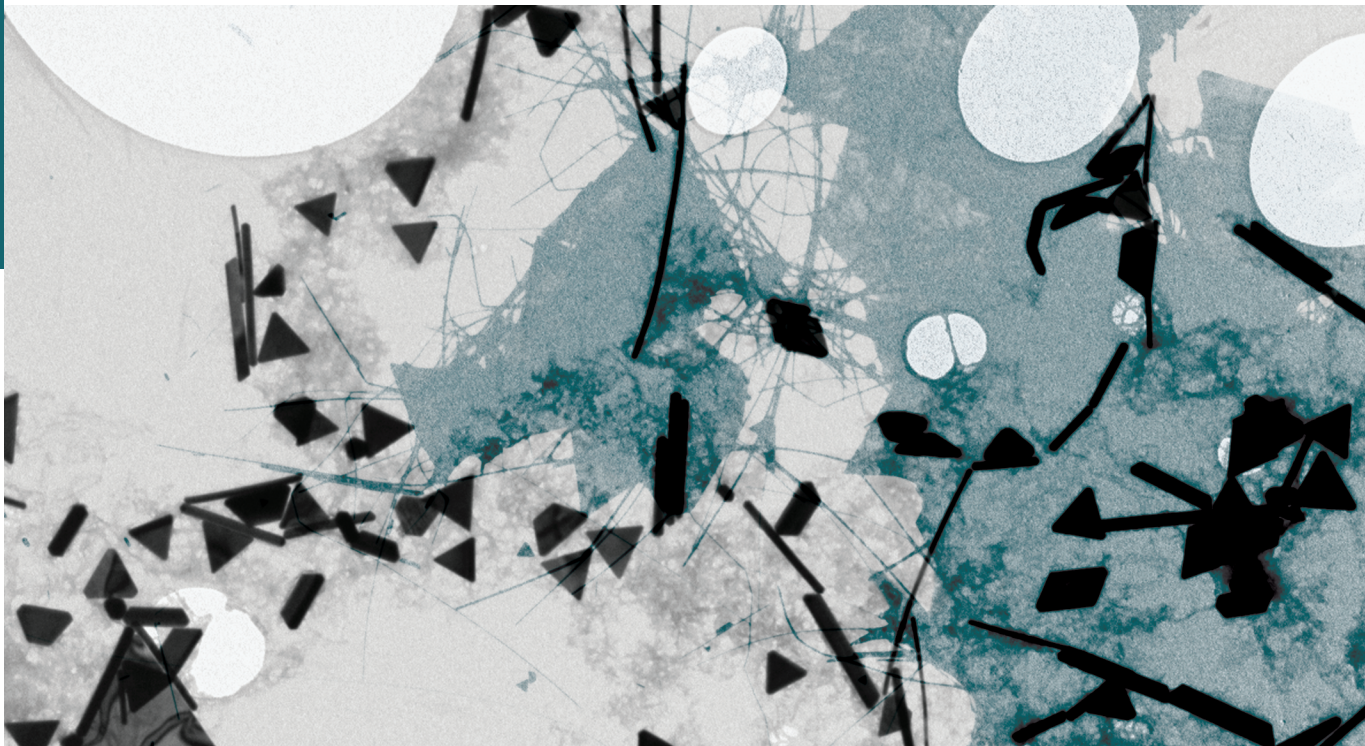
But when irradiating, one has to consider not only hard X-ray or gamma-ray radiotherapy. **Heated Nanoprobes to Destroy Breast Cancer Cells in Mice** [51]. In experiments with laboratory mice that bear aggressive human breast cancers, researchers have used hot nanoprobes to slow the growth of tumors - without damage to surrounding healthy tissue. "We have demonstrated that the system is feasible in laboratory mice. The next step will be clinical testing in patients". Many researchers have studied heat as a potential treatment for cancer, but the difficulty of confining heat within the tumor and predicting an effective heat dose has limited its use. The experimental system uses

bioprobes created by wedding magnetized iron-oxide nanospheres to radiolabeled monoclonal antibodies. The bioprobes are cloaked in polymers and sugars that render them nearly invisible to the body's immune system."Using heat to kill cancer cells isn't a new concept, the biggest problems have been how to apply it to the tumor alone, how to predict the amount needed and how to determine its effectiveness. By combining nanotechnology, focused therapy and quantitative molecular imaging techniques, we have developed a safer technique that could join other modalities as a treatment for breast and other cancers."

And of course, combining radio and chemotherapy, as in "New ovarian cancer treatment succeeds in the lab" [52] A novel way to deliver cancer-killing drugs using nanotechnology completely destroying the tumor within 24 hours, while sparing normal ovarian cells. In lab experiments, Taxol, a chemotherapy drug used to treat ovarian cancer, was loaded onto a magneto-electric nanoparticle, and using an electric field the drug penetrated into the tumor cells completely destroying the tumor within 24 hours, while sparing normal ovarian cells. "Sparing healthy cells has been a major challenge in the treatment of cancer, especially with the use of Taxol; so in addition to treating the cancer, this could have a huge impact on side-effects and toxicity. Ovarian cancer is the deadliest of all gynecological cancers. According to the American Cancer Society 14,000 women will die this year from ovarian cancer. This new treatment is the collaborative product of an oncologist and an engineer looking to challenge the odds and save lives.

And not to forget, that the difference between imaging and radio treatment is basically a question of the power of the incoming beam, thus, [advanced magnetic sensing](#) [53] technology is used to increase access to the standard of care in breast cancer staging by providing an alternative approach to locating sentinel lymph nodes.

Generic



With such promises in the research labs, social events and education on nanooncology has also grown side by side, as the 10s of thousands view of the **Video Journey Into Nanotechnology** [54]. In the fight against cancer, nanotechnology introduces unique approaches to diagnosis and treatment that could not even be imagined with conventional technology. New tools engineered at sizes much smaller than a human cell will enable researchers and clinicians to detect cancer earlier, treat it with much greater precision and fewer side effects, and possibly stop the disease long before it can do any damage: Imagine a nanoparticle that can be used to light up a tumor in an MRI, destroy cancer cells by converting magnetic fields into heat, and allow the physician to visually track the progress of treatment. To learn more about the possibilities of nanotechnology in cancer and explore the field, a Video Journey into Nanotechnology was brought by the National Cancer Institute (NCI), part of the National Institutes of Health, engaged in efforts to harness the power of nanotechnology to radically change the way

we diagnose, treat and prevent cancer. And, on the screens, we have also to celebrate the **First Nanomedicine TV** [55]. Nanomed TV foresees to become the main hub for Nanomedicine thanks to its initiators, two major European players in nanomedicine: the **European Technology Platform on Nanomedicine** (ETPN) [56] and **Nanobiotix** [57]. **Nanomed TV** [58] will make information accessible, aiming at answering what people need and wish to know about Nanomedicine. NanomedTV is supported by renowned experts that bring together scientific, medical, regulatory, industrial and financial expertise. “People are looking for experts to advise them, not to ignore them. Thus, nanomedicine experts need to inform in a trustful and comprehensive way on discoveries and new knowledge in order to speed up the adoption of nanomedicine to the benefit of patients and the healthcare system.” “NanomedTV will contribute to the dissemination of novel medical approaches and will help to bring the interested communities - industry, academia, research bodies and public authorities as well as the individual patients -

together and by that to create a transparent and reliable information channel.” Nanotechnologies represent a historical break that gives clinicians new tools in the fight against disease, trauma and other medical problems. Diagnoses can be made earlier and more quickly; medicines and other treatments can be better targeted and lead to fewer side effects. More importantly, nanomedicine can bring new options for treatment through new modes of action that are not based on biological interaction.

Or the **Nano World Cancer Day: How Nanomedicine Contributes to Better Cancer Diagnostic and Therapy** [59]. A European multi-sites event in Paris, Braga and Berlin. In the framework of the World Cancer Day, the European Technology Platform of Nanomedicine (ETPN) and its partners organize an event on “How nanomedicine contributes to better cancer diagnostic and therapy”. Similar and simultaneous events will be organized in France and Portugal, highlighting the importance of nanomedicine research for cancer on the European level. Radiotherapy, chemotherapy and surgery are part of the therapeutic arsenal for patients with cancer. New technologies associated with nanoparticles could provide more effective solutions to personalize diagnoses and treat these diseases, while improving targeted drug delivery and reducing side effects and collateral damages on the body. These breakthrough therapies based on nanomedicine are already a reality with concrete results, 60 nano-products on the market and more than 70 in the pipeline. Nanomedicine can go further in bringing new therapeutic mode of action into cells. For instance, nanoparticles can already be injected into the tumor and then be activated to produce a physical effect and destroy cancer cells locally. In the press events across Europe, leading international stakeholders in the field will introduce examples highlighting the key role of nanomedicine for cancer therapy, diagnoses and imaging. And also it has reached the crowdsourcing mechanisms, as in NanoDoc. **NanoDoc** [60] is an online game that allows bioengineers and the general public to design new nanoparticle strategies towards the treatment of cancer.

All in all leading to a compilation of the **Lessons Learned in Creating Biomedical Nanoparticles for Human Use** [61]. Over the past six years, the National Cancer Institute’s (NCI) **Nanotechnology Characterization Laboratory** (NCL) [62], a key component of the NCI’s Alliance for Nanotechnology in Cancer, has characterized more than 250 different nanomaterials developed by over 75 research groups. This extensive experience has given NCL staff a unique perspective on how to design safe and biocompatible nanomaterials for human use. In a paper the NCL team shared some of the lessons they have learned. The NCL performs and standardizes the pre-clinical characterization of nanomaterials intended for cancer therapeutics and diagnostics developed by researchers from academia, government, and industry. The Lab serves as a national resource and knowledge base for cancer researchers, and facilitates the development and translation of nanoscale particles and devices for clinical applications. One important lesson for nanomaterial developers, who tend to be academic researchers with little experience developing products intended for clinical use, is that they need to focus more on ensuring that the materials they develop for testing in animals, and eventually humans, are sterile. A recent review of 75 samples arriving at the NCL for testing found that more than one-third showed evidence of bacterial contamination. Another important lesson was that commercially available materials, whether they are nanomaterials or chemicals used to make nanomaterials, are not always what they appear to be. In some cases, these raw materials are contaminated with bacterial toxins, in other cases the products do not meet the specifications advertised by the manufacturers, “it is in the researchers’ best interest to always characterize materials before proceeding with synthesis and more expensive functionalization and biological testing.” NCL staff also found that investigators need to do a better job purifying their nanomaterials of residue remaining from the processes they use to manufacture their nanoparticles and other formulations. In some cases, nanomaterials that appeared to be toxic were in fact biocompatible. Instead, it was production impurities that were causing toxicity issues. Additionally, NCL studies

have shown that nanomaterial toxicity can often be eliminated by choosing slightly different starting materials that are incorporated into the final product but that do not play a role as an imaging agent or anticancer drug.

The last two lessons have to do with the importance of developing the right methods for assessing a nanomaterial's stability in the body and the rate at which it releases its cargo at the intended target, the tumor. NCL team leaders recommend that nanomaterial developers employ multiple assays before beginning animal studies to determine these characteristics of their nanomaterials because single assays can often paint an incomplete picture that can lead to wasted time and money. This is also described in the common pitfalls in nanomedicines: ["Federal Lab Helps Clients Move Prospective Nanomedicines Into Clinical Trials"](#) [63] Nanotechnology Characterization Laboratory accepts about 12 nanomedicine hopefuls each year from academic teams, companies, and government labs in the U.S. for preclinical evaluation—free of charge.

And this also leads to a better **Understanding How Cells Respond to Nanoparticles** [64]: Gold nanoparticles are showing real promise as vehicles for efficiently delivering therapeutic nucleic acids, such as disease-fighting genes and small interfering RNA (siRNA) molecules, to tumors. Now, researchers have shown that the safety of gold nanoparticle-nucleic acid formulations depends significantly on how the nucleic acids and nanoparticles are linked to one another, a finding with important implications for those researchers developing such constructs. To measure how cancer cells respond when they take up nanoparticles, researchers used a technique known as genome-wide expression profiling, which measures relative changes in global gene expression. The investigators added different types of nanoparticles to cancer cells growing in culture dishes and then obtained whole genome expression profiles for the cells. In all the experiments, the researchers attached non-targeting nucleic acids attached to the nanoparticles in order to minimize gene changes that might be triggered through a

therapeutic effect relating to a specific, designed interaction between the nucleic acid and a targeted gene. The results of these comparison studies showed that the surface properties of the nanoparticles had a profound impact on how a given nanoparticle impacts gene expression within a cell. The researchers observed the most surprising and noteworthy difference when they compared two nanoparticles that differed only in the manner in which the nucleic acids were attached to the nanoparticle surface. Nanoparticles loosely linked to the nucleic acids triggered large-scale changes in gene expression, while in contrast, nanoparticles linked tightly to nucleic acids through a covalent chemical bond had virtually no effect on gene expression. These findings, the researchers noted, show how important it is to fully characterize nanoparticles not only in terms of the shape and size, but also with respect to their surface properties.

It is clear, that one of the ways that nanotechnology may contribute to medical sciences is to couple with other innovative therapies which were developed recently and that are now being translated to the clinic. This approaches, as gene therapy, immunotherapy or stem cells therapy have still problems to solve, especially in delivery, and are fields much more permeable and susceptible to incorporate new tools based on nanoparticles, to absorb or distribute photons, oxidize or reduce, accumulate and transport drugs. For example, Gene regulation technology with nanotherapeutics that can cross blood-brain barrier: [Incurable Brain Cancer Gene Is Silenced Designed](#) [65] to target a specific cancer-causing gene in cells, the drug simply flips the switch of the troublesome oncogene to "off," silencing the gene. This knocks out the proteins that keep cancer cells immortal. Another example of this conjunction is the **First Synthetic Organ Transplant** [66]. For the first time in history, a patient has been given a new trachea made from a synthetic scaffold seeded with his own stem cells. The operation was performed at Karolinska University Hospital (Stockholm, Sweden), the University College London, designed and built the nanocomposite tracheal scaffold and Harvard produced a specifically designed bioreactor used

to seed the scaffold with the patient's own stem cells. This was accomplished using a Computerised Tomography scan of the patient as a guide, to create the exact shape and dimension needed. A mould was then made using glass. The patient, a 36-year old man who had been suffering from late stage tracheal cancer, that before this surgery would have been inoperable, is well on the way to a full recovery and was discharged from the hospital. The successful transplantation of tissue engineered synthetic organs, referred to as regenerative medicine, could open new and very promising therapeutic possibilities for the thousands of patients who suffer from tracheal cancer or other conditions that destroy, block or constrict the airway. Transplantations of tissue engineered windpipes with synthetic scaffolds in combination with the patient's own stem cells as a standard procedure, means that patients will not have to wait for a suitable donor organ. The windpipe (trachea) implanted in this patient was developed using a [Novel Nanocomposite Polymer](#) [67]. The materials have other potential uses such as coronary stents and grafts.

The amazing thing is when the implants can be used as a [Nano-Implant Measures Tumor Growth and Treats It](#) [68]. A tiny implant now being developed could one day help doctors rapidly monitor the growth of tumors and the progress of chemotherapy in cancer patients. The implant contains nanoparticles that can be designed to test for different substances, including metabolites such as glucose and oxygen that are associated with tumor growth. It can also track the effects of cancer drugs: Once inside a patient, the implant could reveal how much of a certain cancer drug has reached the tumor, helping doctors determine whether a treatment is working in a particular patient. Such nanoparticles have been used before, but for the first time, researchers have encased the nanoparticles in a silicone delivery device, allowing them to remain in patients' bodies for an extended period of time. The device can be implanted directly into a tumor, allowing researchers to get a more direct look at what is happening in the tumor over time. The new technique, known as implanted magnetic sensing, makes use of detection

nanoparticles composed of iron oxide and coated with a sugar called dextran. Antibodies specific to the target molecules are attached to the surface of the particles. When the target molecules are present, they bind to the particles and cause them to clump together. That clumping can be detected by MRI (magnetic resonance imaging). Similarly, in ["New nanoparticle delivers, tracks cancer drugs"](#) [69] a new iron oxide nanoparticle that delivers cancer drugs to cells while simultaneously monitoring the drug release in real time have been synthesized. This represents an important development for the emerging field of theranostics – a term that refers to nanoparticles that can treat and diagnose disease.

Nanotechnology may also help in the drug discovery by manipulating DNA. [Drag-and-Drop DNA](#) [70]. Using a simple "drag-and-drop" computer interface and DNA self-assembly techniques, researchers have developed a new approach for drug development that could drastically reduce the time required to create and test medications. Researchers recently developed and began evaluating a drug for combating the lethal brain cancer glioblastoma multiforme. "We can now 'print,' molecule by molecule, exactly the compound that we want, what differentiates our nanotechnology from others is our ability to rapidly, and precisely, specify the placement of every atom in a compound that we design." "Currently, most drugs are developed using a screening technique where you try a lot of candidate compounds against targets to 'see what sticks'. Instead, we're designing very specific drugs based on their molecular structure, with target molecules that bind to receptors on specific types of cancer cells. In plug-and-play fashion, we can swap in or swap out any of the functional components, as needed, for a range of treatment approaches."

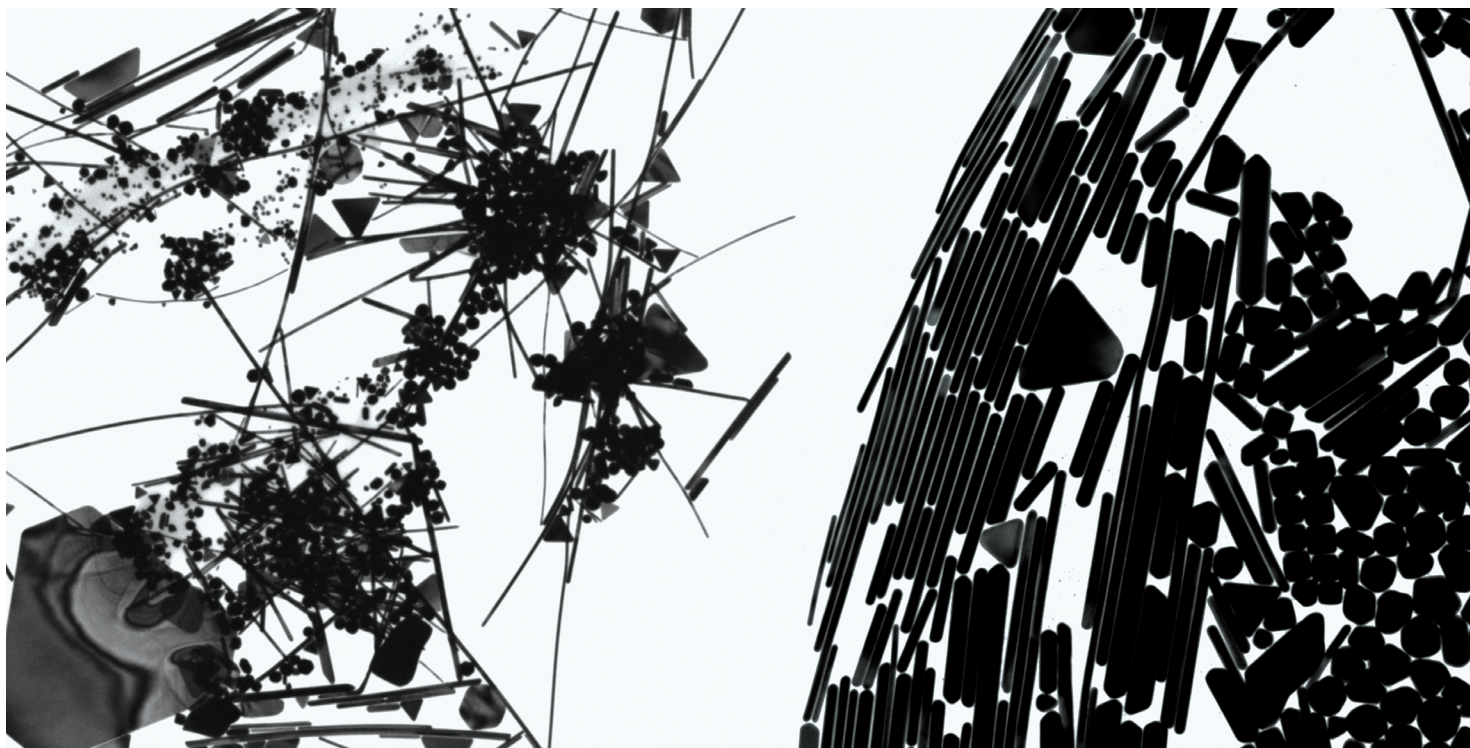
And sophistication may bring today's simple nanotechnologies (one nanoparticle and one drug) to advanced engineered nanobots as in the case of [Flagellated Bacterial Nanorobots for Medical Interventions in the Human Body](#) [71]. A combination of various types of nanorobots will prove to be more important as we

attend to enhance targeting in the smallest blood vessels found in the human microvasculature. As such, various interdependent concepts for the implementation of these different types of medical bio-nanorobots including nanorobots propelled in the microvasculature by flagellated bacteria to target deep regions in the human body. Through experimental results and theoretical formulations, researchers showed the advantages of integrating biological components and more specifically [Magnetotactic Bacteria](#) [72] for the development of hybrid (made of synthetic and biological components) nanorobots adapted to operate in the human microvasculature. Researchers also showed a method capable to track using MRI as imaging modality, steerable microbeads and the magnetotactic bacteria that could be integrated in the implementation of future sophisticated bionanorobots operating inside the complex vascular network. As such, researchers showed that these nanorobots, including the ones propelled by a single flagellated bacterium, could be guided or controlled directly towards specific locations deep inside the human body. We also show experimentally that flagellated bacterial nanorobots could be propelled and steered in vivo through the interstitial region of a tumor for enhanced therapeutic results.

And many other benefits can be enabled by nanotechnology as the [Pills of the future: nanoparticles](#) [73]. Researchers design drug-carrying nanoparticles that can be taken orally. Drugs delivered by nanoparticles hold promise for targeted treatment of many diseases, including cancer. However, the particles have to be injected into patients, which has limited their usefulness so far. Now, researchers have developed a new type of nanoparticle that can be delivered orally and absorbed through the digestive tract, allowing patients to simply take a pill instead of receiving injections. Researchers used the particles to demonstrate oral delivery of insulin in mice, but they say the particles could be used to carry any kind of drug that can be encapsulated in a nanoparticle. The new nanoparticles are coated with antibodies that act as a key to unlock receptors found on the surfaces of cells that line the intestine, allowing

the nanoparticles to break through the intestinal walls and enter the bloodstream. This type of drug delivery could be especially useful in developing new treatments for conditions such as high cholesterol or arthritis. Patients with those diseases would be much more likely to take pills regularly than to make frequent visits to a doctor's office to receive nanoparticle injections, say the researchers. "If you were a patient and you had a choice, there's just no question: Patients would always prefer drugs they can take orally," No more injections. Several types of nanoparticles carrying chemotherapy drugs or short interfering [RNA](#) [74], which can turn off selected genes, are now in clinical trials to treat cancer and other diseases. These particles exploit the fact that tumors and other diseased tissues are surrounded by leaky blood vessels. After the particles are intravenously injected into patients, they seep through those leaky vessels and release their payload at the tumor site. For nanoparticles to be taken orally, they need to be able to get through the intestinal lining, which is made of a layer of epithelial cells that join together to form impenetrable barriers called tight junctions. "The key challenge is how to make a nanoparticle get through this barrier of cells. Whenever cells want to form a barrier, they make these attachments from cell to cell, analogous to a brick wall where the bricks are the cells and the mortar is the attachments, and nothing can penetrate that wall." Researchers have previously tried to break through this wall by temporarily disrupting the tight junctions, allowing drugs through. However, this approach can have unwanted side effects because when the barriers are broken, harmful bacteria can also get through. To build nanoparticles that can selectively break through the barrier, the researchers took advantage of previous work that revealed how babies absorb antibodies from their mothers' milk, boosting their own immune defenses. Those antibodies grab onto a cell surface receptor called the FcRN, granting them access through the cells of the intestinal lining into adjacent blood vessels. The researchers coated their nanoparticles with Fc proteins — the part of the antibody that binds to the FcRN receptor, which is also found in adult intestinal cells. The nanoparticles, made of a biocompatible polymer called PLA-PEG, can carry a large drug

payload, such as insulin, in their core. After the particles are ingested, the Fc proteins grab on to the FcRN in the intestinal lining and gain entry, bringing the entire nanoparticle along with them. “It illustrates a very general concept where we can use these receptors to traffic nanoparticles that could contain pretty much anything. Any molecule that has difficulty crossing the barrier could be loaded in the nanoparticle and trafficked across”. The researchers’ discovery of how this type of particle can penetrate cells is a key step to achieving oral nanoparticle delivery. Nanoparticles coated with Fc proteins reached the bloodstream 11-fold more efficiently than equivalent nanoparticles without the coating. The amount of insulin delivered was large enough to lower the mice’s blood sugar levels. Researchers now hope to apply the same principles to designing nanoparticles that can cross other barriers, such as the blood-brain barrier, which prevents many drugs from reaching the brain. “If you can penetrate the mucosa in the intestine, maybe next you can penetrate the mucosa in the lungs, maybe the blood-brain barrier, maybe the placental barrier.”



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[70] Drag-and-Drop DNA.
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[71] Flagellated Bacterial Nanorobots for Medical Interventions in the Human Body.
See this capsule in page 136.

[72] Magnetotactic Bacteria.
http://en.wikipedia.org/wiki/Magnetotactic_bacteria

[73] Pills of the future: nanoparticles.
<http://newsoffice.mit.edu/2013/nonoparticle-pills-1127>

[74] Explained: RNA interference.
<http://newsoffice.mit.edu/2009/explained-rna>



Nano-Oncology, the Turning Point

PART III **Nanowiki News**

News edited by Josep Saldaña (unless otherwise specified).

Nanoparticles Closer and Closer of Cancer Therapy

Víctor Puentes. October 4, 2008.

Tags: Nanoparticles, Nano-Oncology, Nanomedicine.



“Nanoparticles provide opportunities for designing and tuning properties that are not possible with other types of therapeutics, and as more clinical data become available, the nanoparticle approach should improve further as the optimal properties are elucidated. **Nanoparticle-based therapeutics** are evolving, and newer, more sophisticated multifunctional nanoparticles are reaching the clinic. Results from these trials are already fuelling enthusiasm for this type of therapeutic modality.

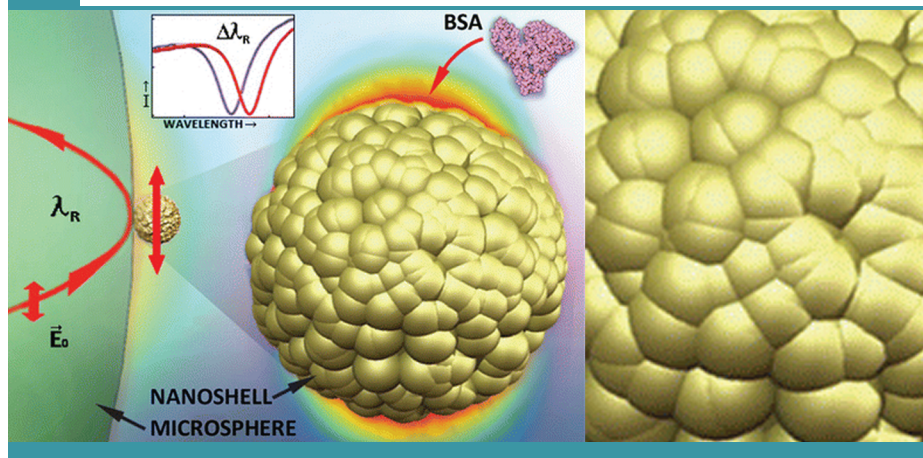
Nanoparticles — particles in the size range 1–100 nm — are emerging as a class of therapeutics for cancer. Early clinical results suggest that nanoparticle therapeutics can show **enhanced efficacy, while simultaneously reducing side effects, owing to properties such as more targeted localization in tumours and active cellular uptake**. Here, we highlight the features of nanoparticle therapeutics that distinguish them from previous anticancer therapies, and describe how these features provide the potential for therapeutic effects that are not achievable with other modalities. While large numbers of preclinical studies have been published, the emphasis here is placed on preclinical and clinical studies that are likely to affect clinical investigations and their implications for advancing the treatment of patients with cancer”.

Source: Nanoparticle therapeutics: an emerging treatment modality for cancer by Mark E. Davis, Zhuo (Georgia) Chen and Dong M. Shin. Nature Reviews Drug Discovery, September 2008

Biosensor to Detect a Single Cancer Marker Protein

July 25, 2013.

Tags: Milestone, Detection, Plasmon, Nano-Oncology, Drug Delivery.



Researchers illustrate the novel way they detected the BSA protein found in blood -- even smaller than a single cancer marker. As the BSA protein lands on the gold nanoshell that is attached to a microcavity, the bumpy gold sphere acts as a nano-amplifier of the interaction, leading to an enhanced shift in the cavity's resonance frequency. The charted waves show how the light wavelength shifts (red) once the BSA molecule lands on the nanoshell. Credit: Polytechnic Institute of New York University.

Just months after setting a record for detecting the smallest single virus in solution, researchers at the Polytechnic Institute of New York University (NYU-Poly) have announced a new breakthrough: They used a nano-enhanced version of their patented microcavity biosensor to detect a single cancer marker protein, which is one-sixth the size of the smallest virus, and even smaller molecules below the mass of all known markers. This achievement shatters the previous record, setting a new benchmark for the most sensitive limit of detection, and may significantly advance early disease diagnostics. Unlike current technology, which attaches a fluorescent molecule, or label, to the antigen to allow it to be seen, the new process detects the antigen without an interfering label.

In 2012, Stephen Arnold, university professor of applied physics and member of the Othmer-Jacobs Department of Chemical and Biomolecular Engineering, and his team were able to detect in solution the smallest known RNA virus, MS2, with a mass of 6 attograms. Now, with experimental work by postdoctoral fellow Venkata Dantham and former student David Keng, two proteins have been detected: a human cancer marker protein called Thyroglobulin, with a mass of just 1 attogram, and the bovine form of a common plasma

protein, serum albumin, with a far smaller mass of 0.11 attogram. "An attogram is a millionth of a millionth of a millionth of a gram," said Arnold, "and we believe that our new limit of detection may be smaller than 0.01 attogram."

This latest milestone builds on a technique pioneered by Arnold and collaborators from NYU-Poly and Fordham University. In 2012, the researchers set the first sizing record by treating a novel biosensor with plasmonic gold nano-receptors, enhancing the electric field of the sensor and allowing even the smallest shifts in resonant frequency to be detected. Their plan was to design a medical diagnostic device capable of identifying a single virus particle in a point-of-care setting, without the use of special assay preparations.

At the time, the notion of detecting a single protein—phenomenally smaller than a virus—was set forth as the ultimate goal.

"Proteins run the body," explained Arnold. "When the immune system encounters virus, it pumps out huge quantities of antibody proteins, and all cancers generate protein markers. **A test capable of detecting a single protein would be the most sensitive diagnostic test imaginable.**"

To the surprise of the researchers, examination of their nanoreceptor under a transmission electron microscope revealed that its gold shell surface was covered with random bumps roughly the size of a protein. Computer mapping and simulations created by Stephen Holler, once Arnold's student and now assistant professor of physics at Fordham University, showed that these irregularities generate their own highly reactive local sensitivity field extending out several nanometers, amplifying the capabilities of the sensor far beyond original predictions. "A virus is far too large to be aided in detection by this field," Arnold said. "Proteins are just a few nanometers across—exactly the right size to register in this space."

The implications of single protein detection are significant and may lay the foundation for improved medical therapeutics. Among other advances, Arnold and his colleagues posit that the ability to follow a signal in real time—to actually witness the detection of a single disease marker protein and track its movement—may yield new understanding of how proteins attach to antibodies.

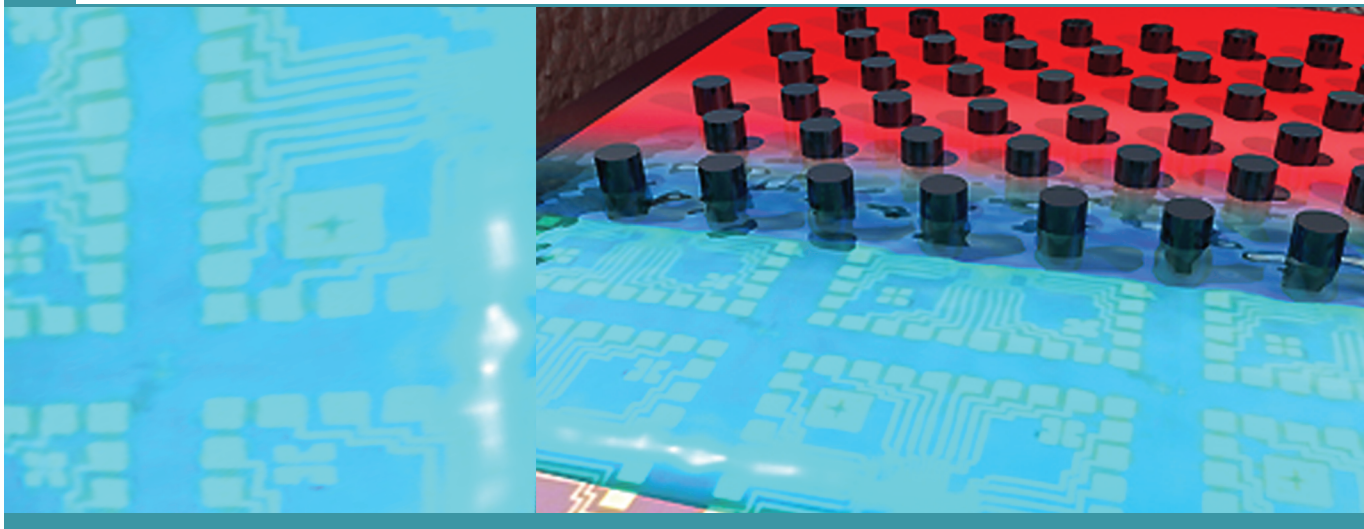
Arnold named the novel method of label-free detection "whispering gallery-mode biosensing" because light waves in the system reminded him of the way that voices bounce around the whispering gallery under the dome of St. Paul's Cathedral in London. A laser sends light through a glass fiber to a detector. When a microsphere is placed against the fiber, certain wavelengths of light detour into the sphere and bounce around inside, creating a dip in the light that the detector receives. When a molecule like a cancer marker clings to a gold nanoshell attached to the microsphere, the microsphere's resonant frequency shifts by a measureable amount.

Source: NYU-Poly Nano Scientists Reach the Holy Grail in Label-Free Cancer Marker Detection: Single Molecules. This work is detailed in the paper "Label-Free Detection of Single Protein Using a Nanoplasmonic-Photonic Hybrid Microcavity" by Venkata R. Dantham, Stephen Holler, Curtis Barbre, David Keng, Vasily Kolchenko, and Stephen Arnold.

First Use of Label-Free Nanosensors with Physiological Solutions

December 21, 2009.

Tags: Nanomedicine, Nano-Oncology, Detection, Nanoelectronics.



Blood is filtered and transferred to nanosensors on a chip, which can detect and measure cancer biomarkers. Photo: Mark Reed.

A team led by Yale University researchers has used nanosensors to measure cancer biomarkers in whole blood for the first time. Their findings could dramatically simplify the way physicians test for biomarkers of cancer and other diseases.

The team—led by Mark Reed, Yale's Harold Hodgkinson Professor of Engineering & Applied Science, and Tarek Fahmy, an associate professor of biomedical and chemical engineering—used nanowire sensors to detect and measure concentrations of two specific biomarkers: one for prostate cancer and the other for breast cancer.

“Nanosensors have been around for the past decade, but they only worked in controlled, laboratory settings,” Reed said. “This is the first time we’ve been able to use them with whole blood, which is a complicated solution containing proteins and ions and other things that affect detection.”

To overcome the challenge of whole blood detection, the researchers developed a novel device that acts as a filter, catching the biomarkers—in this case, antigens specific to prostate and breast cancer—on

a chip while washing away the rest of the blood. Creating a buildup of the antigens on the chip allows for detection down to extremely small concentrations, on the order of picograms per milliliter, to within an accuracy of plus or minus 10 percent. This is the equivalent of being able to detect the concentration of a single grain of salt dissolved in a large swimming pool.

Until now, detection methods have only been able to determine whether or not a certain biomarker is present in the blood at sufficiently high concentrations for the detection equipment to give reliable estimates of its presence. “This new method is much more precise in reading out concentrations, and is much less dependent on the individual operator’s interpretation,” Fahmy said.

In addition to relying on somewhat subjective interpretations, current tests are also labor intensive. They involve taking a blood sample, sending it to a lab, using a centrifuge to separate the different components, isolating the plasma and putting it through an hours-long chemical analysis. The whole process takes several days. In comparison, the new device is able to read out biomarker concentrations in just

a few minutes.

“Doctors could have these small, portable devices in their offices and get nearly instant readings,” Fahmy said. “They could also carry them into the field and test patients on site.”

The new device could also be used to test for a wide range of biomarkers at the same time, from ovarian cancer to cardiovascular disease, Reed said. “The advantage of this technology is that it takes the same effort to make a million devices as it does to make just one. We’ve brought the power of modern microelectronics to cancer detection.”

Source: Scientists Use Nanosensors for First Time to Measure Cancer Biomarkers in Blood. This work is detailed in the paper “**Label-free biomarker detection from whole blood**” by Eric Stern, Aleksandar Vacic, Nitin Rajan, Jason Criscione, Jason Park, Mark Reed and Tarek Fahmy (all of Yale University); Bojan Ilic (Cornell University); David Mooney (Harvard University).

Diagnosis Through Breath

May 14, 2009.

Tags: Detection, Nanomedicine, Nano-Oncology.



In 2006 researchers established that dogs could detect cancer by sniffing the exhaled breath of cancer patients. Now, using nanoscale arrays of detectors, two groups of investigators have shown that a compact mechanical device also can **sniff out lung cancer in humans**. Hossam Haick, Ph.D., and his colleagues at the Israel Institute of Technology in Haifa, used a network of 10 sets of chemically modified carbon nanotubes to create a multicomponent sensor capable of discriminating between a healthy breath and one characteristic of lung cancer patients. Meanwhile, Silvano Dragonieri, M.D., University of Bari, Italy, and his colleagues used a commercial nanoarray-based electronic “nose” to discriminate between the breath of patients with non-small cell lung cancer and chronic obstructive pulmonary disease (COPD). [Source: Nanosensor Arrays “Smell” Cancer.](#) The results of Dr. Haick’s team’s work appear in the paper Detection of nonpolar molecules by means of carrier scattering in random networks of carbon nanotubes: Toward diagnosis of diseases via breath samples. Dr. Dragneri and his colleagues published their work in the paper An electronic nose in the discrimination of patients with non-small cell cancer and COPD

“Blood tests and urinalysis are the golden standard to identify a decline in kidney filtration, wherein high levels of creatinine and blood urea nitrogen usually reflect

renal dysfunction – however, these tests tend to be highly inaccurate and may remain within the normal range even while 65-75% of kidney function is lost.” Hossam Haick tells Nanowerk. “Given the difficulties in separating healthy renal function from dysfunction, it is perhaps not too surprising that precise biochemical or clinical criteria for diagnosis of acute renal failure have been elusive. Therefore, there is an unmet need for a noninvasive method for detection of renal failure of various etiologies. Furthermore, the challenge remains to diagnose renal disorders with sufficient sensitivity and specificity to provide a large-scale screening technique, feasible for clinical practice, for people at increased risk of developing renal dysfunction.” Haick, Zaid Abassi and coworkers from Technion used an experimental model of end stage **renal disease (ESRD)** in rats to identify by advanced, yet simple nanotechnology-based approach to discriminate between exhaled breath of healthy states and of ESRD states. [Source: Nanotechnology breath analyzer for kidney failure.](#) This work is detailed in the paper Sniffing Chronic Renal Failure in Rat Model by an Array of Random Networks of Single-Walled Carbon Nanotubes

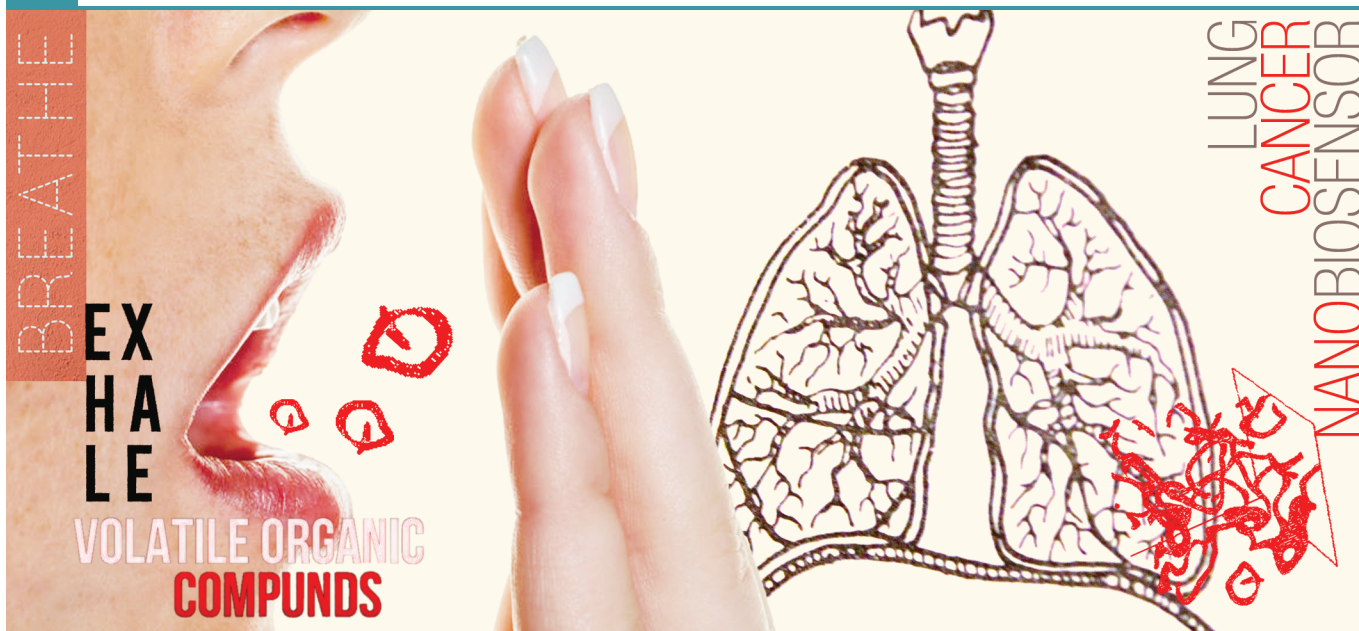
An unlikely multidisciplinary scientific collaboration has discovered that an electronic nose developed for air quality monitoring on Space Shuttle Endeavour can also be used to detect odour differences

in normal and cancerous brain cells. The results of the pilot study open up new possibilities for neurosurgeons in the fight against **brain cancer**. The electronic nose, which is to be installed on the International Space Station in order to automatically monitor the station’s air, can detect contaminants within a range of one to approximately 10,000 parts per million. In a series of experiments, the Brain Mapping Foundation used NASA’s electronic nose to sniff brain cancer cells and cells in other organs. Their data demonstrates that the electronic nose can sense differences in odour from normal versus cancerous cells. These experiments will help pave the way for more sophisticated biochemical analysis and experimentation. Babak Kateb, Chairman and Scientific Director of the Brain Mapping Foundation, is the lead author of the paper set to be published in an IBMISPS-NeuroImage special issue in July. [Source: NASA’s Electronic Nose May Provide Neurosurgeons With A New Weapon Against Brain Cancer](#)

Cheap, Fast, Portable and Performant, Must Be Nanotechnology. Lung Cancer Nanobiosensor

Víctor Puentes. September 4, 2009.

Tags: Detection, Nanoparticles, Nanomedicine, Nano-Oncology.



In miniaturization, mimicking the sense of smell has been a major target. The Smell is composed of thousands integrated specific receptors, in fact, the Smell occupies about a thousand of genes and such a huge analyzing library has to be shrunk to fit in a body. With nanotechnology success is closer. Already, using carbon nanotubes these principles have been tested and verified. Now, changing the material, using gold nanoparticles.

"A highly sensitive and fast-response array of sensors based on gold nanoparticles, in combination with pattern recognition methods, can distinguish between the odor prints of non-small-cell lung cancer and negative controls with 100% accuracy, with no need for preconcentration techniques. Additionally, preliminary results indicate that the same array of sensors might serve as a better tool for understanding the biochemical source of volatile organic compounds that might occur in cancer cells and appear in the exhaled breath, as compared to traditional spectrometry techniques. The reported results provide a launching pad to initiate a bedside tool that

might be able to screen for early stages of lung cancer and allow higher cure rates. In addition, such a tool might be used for the immediate diagnosis of fresh (frozen) tissues of lung cancer in operating rooms, where a dichotomic diagnosis is crucial to guide surgeons."

Source: Sniffing the Unique Odor Print of Non-Small-Cell Lung Cancer with Gold Nanoparticles by Orna Barash, Nir Peled, Fred R. Hirsch, Hossam Haick.

"Conventional diagnostic methods for lung cancer are unsuitable for widespread screening because they are expensive and occasionally miss tumours. Gas chromatography/mass spectrometry studies have shown that several volatile organic compounds, which normally appear at levels of 1–20 ppb in healthy human breath, are elevated to levels between 10 and 100 ppb in lung cancer patients. Here we show that an array of sensors based on gold nanoparticles can rapidly distinguish the breath of lung cancer patients from the breath of healthy individuals in an atmosphere of high humidity. In combination with solid-phase microextraction, gas

chromatography/mass spectrometry was used to identify 42 volatile organic compounds that represent lung cancer biomarkers. Four of these were used to train and optimize the sensors, demonstrating good agreement between patient and simulated breath samples. Our results show that sensors based on gold nanoparticles could form the basis of an inexpensive and non-invasive diagnostic tool for lung cancer."

Source: Diagnosing lung cancer in exhaled breath using gold nanoparticles by Gang Peng, Ulrike Tisch, Orna Adams, Meggie Hakim, Nisreen Shehada, Yoav Y. Broza, Salem Billan, Roxolyana Abdah-Bortnyak, Abraham Kuten & Hossam Haick

New NanoTech Able to Examine Single Molecules

July 1, 2007.

Tags: Nanomedicine, Nano-Oncology.

A new nanotechnology that can examine single molecules in order to determine gene expression, paving the way for scientists to more accurately examine single cancer cells, has been developed by an interdisciplinary team of researchers at UCLA, California Nanosystems Institute (CNSI), New York University Courant Institute of Mathematical Sciences, and Veeco Instruments, a

nanotechnology company.

Previously, researchers have been able to determine gene expression using microarray technology or DNA sequencing. However, such processes could not effectively measure single gene transcripts-the building blocks of gene expression. With their new approach, the researchers of the work

reported in Nanotechnology were able to isolate and identify individual transcript molecules-a sensitivity not achieved with earlier methods.

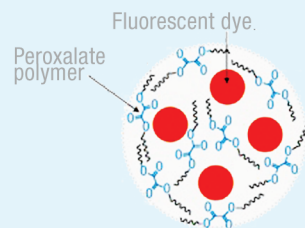
Source: New Nanotechnology Able to Examine Single Molecules, Aiding in Determining Gene Expression.

Nanoparticle Could Help Detect Many Diseases Early

August 20, 2007.

Tags: Nanomedicine, Detection, Nano-Oncology.

The nanoparticle polymer is made of peroxalate esters. A fluorescent dye (pentacene) is then encapsulated into the polymer. When the nanoparticles bump into hydrogen peroxide, they excite the dye, which then emits photons (or light) that can be detected.



Georgia Institute of Technology and Emory University researchers are the first to create a nanoparticle capable of detecting and imaging trace amounts of hydrogen peroxide in animals. The nanoparticles, thought to be completely nontoxic, could some day be used as a simple, all-purpose diagnostic tool to detect the earliest stages of any disease that involves chronic inflammation — everything from cancer and Alzheimer's to heart disease and arthritis.

Source: Nanoparticle Could Help Detect Many Diseases Early

Find Disease Before It Starts

July 15, 2007.

Tags: Nanomedicine, Nano-Oncology, Images.

NanoTechnology may one day help physicians detect the very earliest stages of serious diseases like cancer, a new study suggests.

It would do so by improving the quality of images produced by one of the most common diagnostic tools used in doctors' offices, the UltraSound machine. In laboratory experiments on mice, scientists found that nano-sized particles injected into the animals improved the resulting images. This study is one of the first reports showing that ultrasound can detect these tiny particles when they are inside the body.

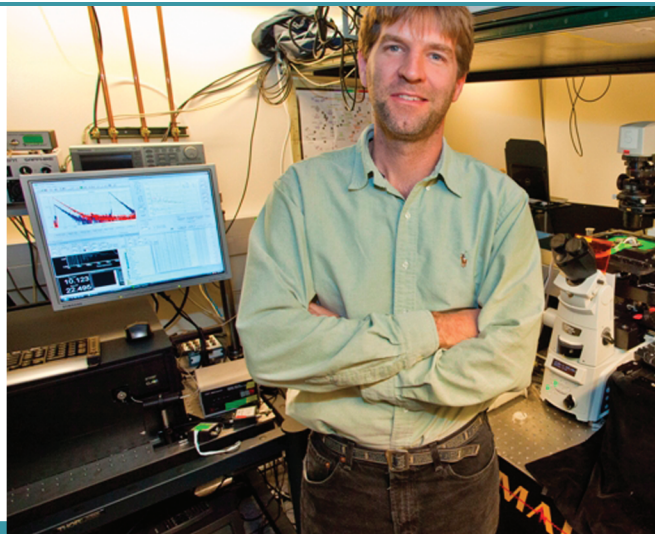
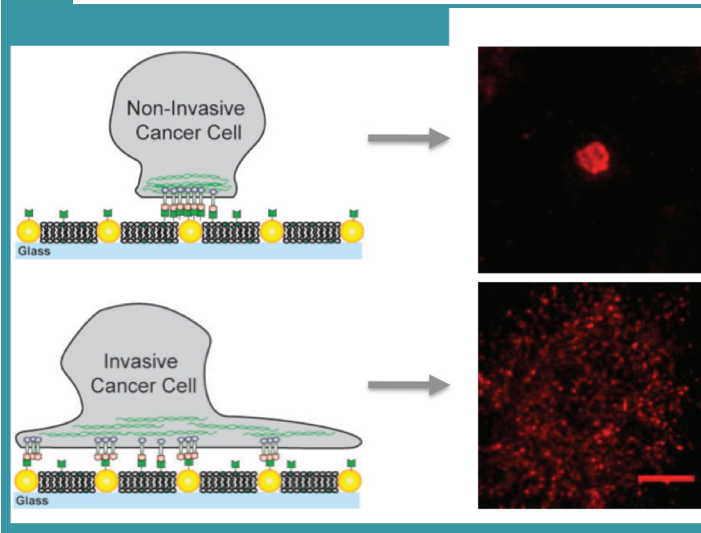
"We ultimately want to identify disease at its cellular level, at its very earliest stage." The hope is that combining ultrasound and nanotechnology may provide a definitive diagnosis in lieu of an invasive procedure like a biopsy.

Source: Nanotechnology May Find Disease Before It Starts

Biomechanical Factor in Malignancies Identified

July 5, 2013.

Tags: Nano-Oncology, Nanomedicine.



On artificial membranes embedded with gold nanodots, non-invasive cancer cells bind only to the nanodots and become immobilized while invasive cells bind to the membrane as well as the nanodots creating mobile clusters that contribute to metastasis. Credit: Groves Lab, Lawrence Berkeley National Laboratory

Jay Groves is a leading authority in the emerging field of mechanobiology, which seeks to understand how cells sense and respond to mechanical forces. (Photo by Roy Kaltschmidt)

Evidence is mounting that the development and spread of cancer, long attributed to gene expression and chemical signaling gone awry, involves a biomechanical component as well. Researchers at Lawrence Berkeley National Laboratory (Berkeley Lab) have added to this body of evidence by demonstrating that the malignant activity of a critical cellular protein system can arise from what essentially are protein traffic jams.

Using a unique artificial membrane imbued with an obstacle course of gold nanodots, a research team led by chemist Jay Groves studied the transport of the protein signaling complex EphA2/ephrin-A1 across the surfaces of 10 different breast epithelial cancer cell lines displaying a wide range of disease characteristics. The researchers found that transport of this receptor-ligand complex was normal in healthier cell lines but became jammed in diseased cell lines, with the worst jamming taking place in the cells that were the most diseased.

Groves is a leading authority in the emerging field of **mechanobiology**, which **seeks**

to understand how cells sense and respond to mechanical forces. To investigate for a possible mechanical factor in EphA2's link to breast cancer, Groves used a technique his group developed in which artificial membranes made up of a fluid bilayer of lipid molecules are embedded with fixed arrays of gold nanodots. This allows researchers to control the spacing or transport of proteins and other cellular molecules placed on the membranes.

For this study, Groves and his colleagues used arrays of gold nanodots to present defined obstacles to the movement and assembly of EphA2/ephrin-A1 clusters. The ephrin-A1 ligands could bind to the membrane, which allowed the clusters to be mobile, or to the nanodots, which immobilized the clusters, or to both. The researchers worked with lines of breast cancer cells that have similar levels of EphA2 expression and included MDA-MB-231, a highly invasive and tumorigenic line, and MCF10A, a relatively benign and non-tumorigenic line.

"When we see cells that have the same

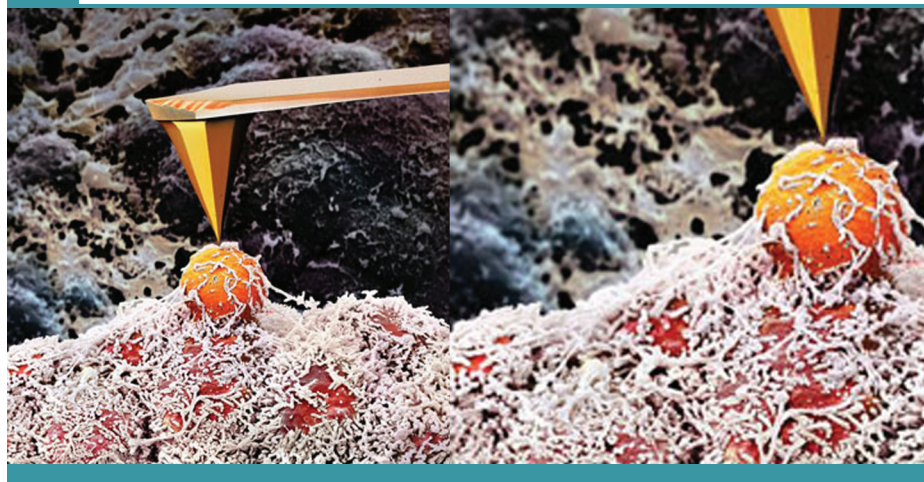
levels of EphA2 but the MDA-MB-231 is jammed while the MCF10A is not, then we can say it is something beyond just the numbers of EphA2 that matters, something about the way EphA2 is plugged into the rest of the cell that is misrelated," Groves says. **"Our observations suggest the cytoskeleton is the culprit and that drugs modulating the cytoskeleton might also therapeutically modulate EphA2 clustering, thereby reducing pathological behavior."**

Source: Cancerous Traffic Jams: Biomechanical Factor in Malignancies Identified by Lynn Yarris. This work is detailed in the paper **"Nanoscale Obstacle Arrays Frustrate Transport of EphA2-Ephrin-A1 Clusters in Cancer Cell Lines"** by Theobald Lohmüller, Qian Xu, and Jay T. Groves.

The Nanomechanical Signature of Breast Cancer

October 24, 2012.

Tags: Nanobiotechnology, Nanomechanics, Detection, Microscope, Nano-Oncology.



Using ARTIDIS to feel the tissue structure of a tumor biopsy by a nanometer-sized atomic force microscope tip. Image: Martin Oeggerli.

The spread of cancer cells from primary tumors to other parts of the body remains the leading cause of cancer-related deaths. The research groups of Roderick Lim and Cora-Ann Schoenenberger from the Biozentrum of the University of Basel, reveal how the unique nanomechanical properties of breast cancer cells are fundamental to the process of metastasis. **The discovery of specific breast cancer “fingerprints” was made using breakthrough nanotechnology known as ARTIDIS.**

Breast cancer is the most common form of cancer in women with 5,500 patients being diagnosed with the disease in Switzerland each year. Despite major scientific advancements in our understanding of the disease, breast cancer diagnostics remains slow and subjective. Here, the real danger lies in the lack of knowing whether metastasis, the spread of cancer, has already occurred. Nevertheless, important clues may be hidden in how metastasis is linked to specific structural alterations in both cancer cells and the surrounding extracellular matrix. This forms the motivation behind **ARTIDIS (“Automated and Reliable Tissue Diagnostics”)**, which was conceived by Dr. med. Marko Loparic, Dr. Marija Plodinec and Prof. Roderick Lim to measure the local nanomechanical properties of tissue biopsies.

“Fingerprinting” breast tumors

At the heart of ARTIDIS lies an ultra-sharp atomic force microscope tip of several nanometers in size that is used as a local mechanical probe to “feel” the cells and extracellular structures within a tumor biopsy. In this way, a nanomechanical “fingerprint” of the tissue is obtained by systematically acquiring tens of thousands of force measurements over an entire biopsy.

Subsequent analysis of over one hundred patient biopsies could confirm that the fingerprint of malignant breast tumors is markedly different as compared to healthy tissue and benign tumors. This was validated by histological analyses carried out by clinicians at the University Hospital Basel, which showed a complete agreement with ARTIDIS. Moreover, the same nanomechanical fingerprints were found in animal studies initiated at the Friedrich Miescher Institute.

Plodinec, first author of the study, explains: “This unique fingerprint reflects the heterogeneous make-up of malignant tissue whereas healthy tissue and benign tumors are more homogenous.” Strikingly, malignant tissue also featured a marked predominance of “soft” regions that is a characteristic of cancer cells and the altered microenvironment at the tumor core. The significance of these findings lies in

reconciling the notion that soft cancer cells can more easily deform and “squeeze” through their surroundings. Indeed, the presence of the same type of “soft” phenotype in secondary lung tumors of mice reinforces the close correlation between the physical properties of cancer cells and their metastatic potential.

ARTIDIS in the clinics

“Resolving such basic scientific aspects of cancer further underscores the use of nanomechanical fingerprints as quantitative markers for cancer diagnostics with the potential to prognose metastasis,” states Loparic, who is project manager for ARTIDIS. On an important practical note, a complete biopsy analysis by ARTIDIS currently takes four hours in comparison to conventional diagnostics, which can take one week. Based on the **potential societal impact of ARTIDIS to revolutionize breast cancer diagnostics**, Lim’s team and the Swiss company Nanosurf AG have now been awarded about 1.2 million Swiss francs by the Commission for Technology and Innovation (CTI) to further develop ARTIDIS into a state-of-the-art device for disease diagnostics with further applications in nanomedicine.

Over the next two years, Lim and colleagues will engage and work closely with clinicians to develop ARTIDIS into an easy-to-use “push-button” application to fingerprint diseases across a wide range of biological tissues. As a historical starting point, the first ARTIDIS demo-lab has already been established at the University Hospital Eye Clinic to collect data on retinal diseases with the goal of improving treatment strategies.

Source: The nanomechanical signature of breast cancer. This work is detailed in the paper “**The nanomechanical signature of breast cancer**” by Marija Plodinec, Marko Loparic, Christophe A. Monnier, Ellen C. Obermann, Rosanna Zanetti-Dallenbach, Philipp Oertle, Janne T. Hyotyla, Ueli Aebi, Mohamed Bentires-Alj, Roderick Y. H. Lim & Cora-Ann Schoenenberger.

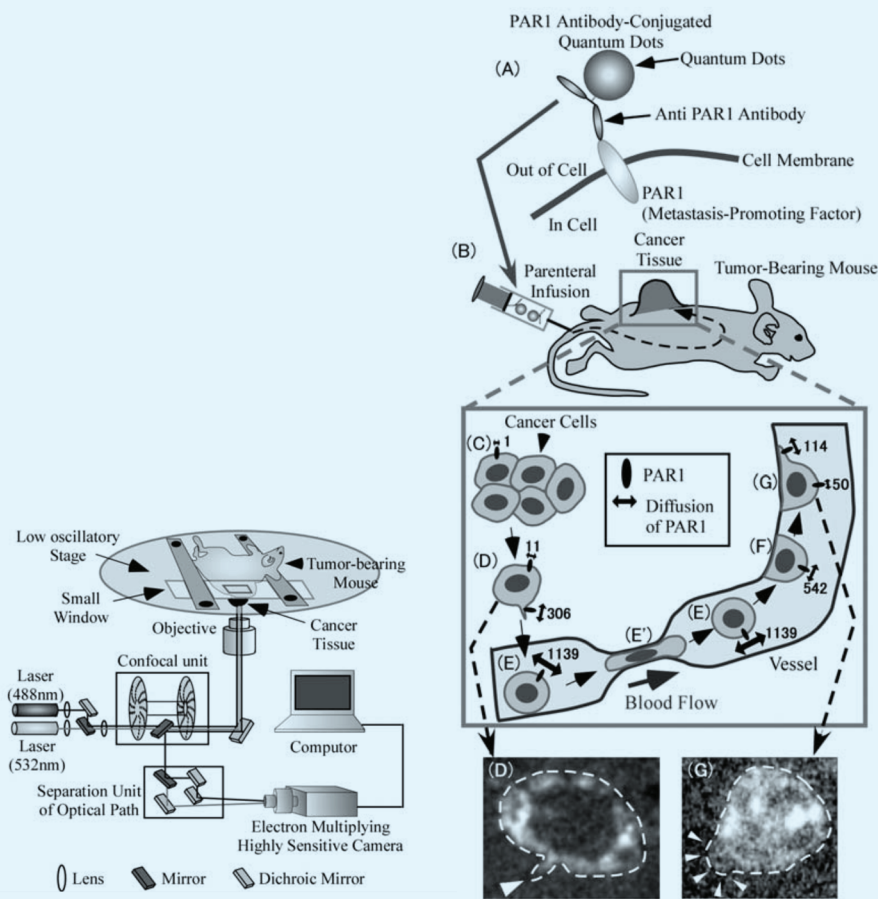
Context:

May 26, 2012. From Mars into the hospital: Detecting Breast Cancer and Osteoarthritis with Nanotechnology Made for Mars June 4, 2008. First Atomic Force Microscope on Mars

Cancer Metastasis Mechanism at Nanometer Level

February 5, 2010.

Tags: Milestone, Nanomedicine, Nano-Oncology, Quantum Dots, Microscope.



Optical system for in vivo imaging.

An outline for methods and results of in vivo imaging of cell membrane dynamics during cancer metastasis.

C-G, Cells in vivo during metastasis. C, Cells far from vessels. D, Cell near vessels. E, Cell in the bloodstream. E', Cells in narrow vessels. F, Cells adhering to the inner vascular surface without directional migration. G, Cells migrating directionally on the surface. The number in C-G means the relative value when the migration speed of PAR1 in the cells far from vessels was defined as 1. The arrowheads in D and G indicate clearly-imaged pseudopodia. Bar, 10 micrometer (D and G). In conclusion, PAR1 migration speed of metastasizing cancer cells increases during intravasation, reaches a peak in the vessel, decreases at extravasation, and is also higher at locally formed pseudopodia. The dramatic changes in membrane protein and morphology enable cancer cells to metastasize.

A research group led by Professor Noriaki Ohuchi, Senior Assistant Professor Kohsuke Gonda at Graduate School of Medicine, Tohoku University and Professor Hideo Higuchi at Graduate School of Science, The University of Tokyo has developed an optical system to image with a spatial precision of 9 nanometer in vivo. The optical system enables to visualize protein and drug at single molecular level in tumor-bearing mice which is implanted with human breast cancer cells. The most terrible biological property of cancer is its ability to spread to other organs. The research group labeled the metastasis-promoting protein on the cell membrane with fluorescence particle and has analyzed the protein dynamics with the newly developed optical device. In this study, they firstly discovered following cancer mechanisms using mice:

1. A change of cell morphology is important for cancer metastasis.
2. Cancer cells showed increases in migration speed (diffusion speed) of membrane protein (over 1000-fold) with progression of metastasis. The change of migration speed is important for activation of cancer metastasis.

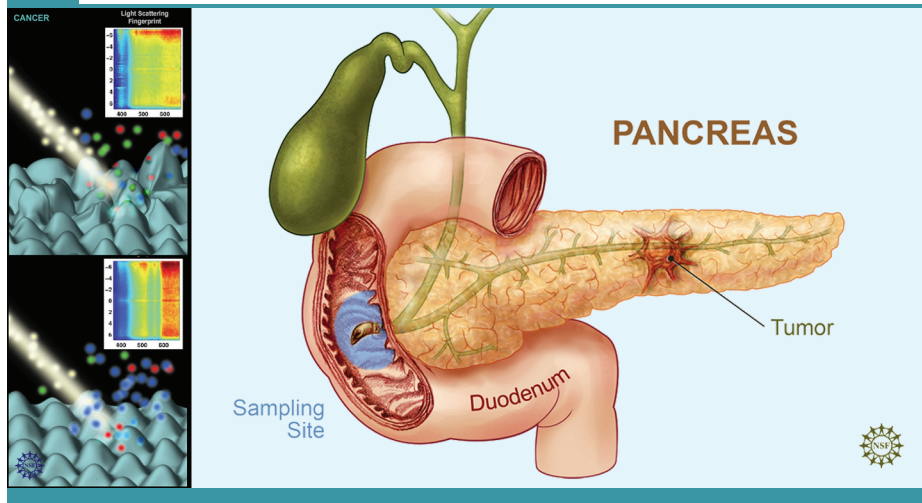
A cancer metastasis mechanism at molecular level has long been unknown because a spatial precision of previous in vivo imaging was at micrometer level. This study enable to visualize the mechanism of cancer metastasis at molecular level. The results are expected to clarify an activation mechanism of cancer metastasis, evaluate malignant grade by measuring membrane protein migration speed, and develop a new treatment with improved anticancer drug.

Source: Visualization of a cancer metastasis mechanism at nanometer level: Discovery of dramatic changes of membrane dynamics in cancer cells during metastasis. This work is detailed in the paper "In vivo nano-imaging of membrane dynamics in metastatic tumor cells using quantum dots" by Kohsuke Gonda, Tomonobu M. Watanabe, Noriaki Ohuchi and Hideo Higuchi.

Nanoscopic Changes to Pancreatic Cells Reveal Cancer

February 24, 2009.

Tags: Nanophotonics, Detection, Nanomedicine, Nano-Oncology, Microscope.



RIGHT

Pancreatic cancer (unseen at its earliest stages by any other methods) can be detected by examining tissue from inside the duodenum, the uppermost section of the small intestine, using new techniques called four-dimensional elastic light scattering fingerprinting (4D-ELF) and low-coherence enhanced backscattering spectroscopy (LEBS). The pancreatic duct communicates with the duodenum via the Ampulla of Vater. Researchers have shown that cells in a roughly three centimeter radius from this feature can show signs of the presence of cancer. Credit: Zina Deretsky, National Science Foundation

LEFT

How light bounces off of human tissue allow to detect subtle changes potentially caused by cancer. Credit: Nicole Rager Fuller, National Science Foundation

A team of researchers in Chicago has developed a way to examine cell biopsies and detect never-before-seen signs of early-stage pancreatic cancer. Though the new technique has not yet proven effective in double-blind clinical trials, it may one day help diagnose cancers of the pancreas and, potentially, other organs at their earliest and most treatable stages, before they spread.

A team from Northwestern University and NorthShore University HealthSystem describes the first application of their new technique, which they call partial wave microscopic spectroscopy. This technique allows them to examine cell samples taken from people who have undergone screening for pancreatic cancer to detect signs of the disease.

Pancreatic cancer is typically diagnosed by hospital pathologists who look for telltale changes to the morphology of pancreatic cells when they examine cell biopsies under the microscope. The problem is that in the early stages of cancer, many early-stage cancer cells appear normal. By the time the cancerous cells undergo observable changes, it may be too late in the disease progression for effective treatment.

In fact, only 7 percent of people with pancreatic cancer are diagnosed in the earliest stages of the disease, when the

cancer is still confined to its primary site. More than half of all people with the disease are not diagnosed until it has already metastasized.

"In the beginning, cells look normal," says Vadim Backman, a professor of biomedical engineering at Northwestern University who developed partial wave microscopic spectroscopy with his former graduate students Yang Liu and Hariharan Subramanian and postdoctoral fellow Prabhakar Pradhan. **The new technique measures nanoscopic changes to the interior architecture of cells — changes that may signal signs of cancer even in cells that look normal under the microscope.**

To test their technique, Backman and Subramanian collaborated with gastroenterologists Hemant K. Roy and Randall Brand, who had collected tissue samples from people undergoing biopsies to detect pancreatic cancer.

The new technique works by detecting fluctuations in the cells' refractive index (an optical property that measures how cells bend light passing through them). No other technique has ever measured this quantitatively, says Backman. These fluctuations are influenced by nanoscopic changes to the cells'

interior architecture that often occur much earlier than the changes pathologists can detect under their microscopes. The more architectural disorder there is inside the cell, the more the refractive index fluctuates. The Chicago researchers showed that by quantifying these fluctuations, partial wave spectroscopy could identify cancer cells even in cases where they had not been detected by pathologists.

Partial wave microscopic spectroscopy may be a boon to medicine, if it proves effective in clinical trials at detecting cancers early — especially for people with pancreatic cancer, which is one of the most deadly forms of cancer. According to the National Cancer Institute, more than 37,000 men and women in the United States were diagnosed with pancreatic cancer in 2008, and statistically 95 percent of them will succumb to the disease within five years.

Source: Nanoscopic changes to pancreatic cells reveal cancer. This work is detailed in the paper "**Partial-wave microscopic spectroscopy detects subwavelength refractive index fluctuations: an application to cancer diagnosis**" by Hariharan Subramanian, Prabhakar Pradhan, Yang Liu, Ilker R. Capoglu, Jeremy D. Rogers, Hemant K. Roy, Randall E. Brand, and Vadim Backman

Gold Nanorods Image Tumors

October 1, 2007.

Tags: Nanomedicine, Nano-Oncology.



Glod Bricks and stones (detail). image by Víctor Puentes.

A growing body of research has demonstrated that gold nanorods can serve as extremely bright imaging agents. Now, by linking gold nanorods to an antibody that binds to tumor cells, researchers have found that gold nanorods will align themselves in an ordered fashion on the surface of cancer cells, further intensifying the optical signal the nanorods produce and providing a unique optical signature for tumor cells.

The work by Mostafa El-Sayed and colleagues is detailed in the paper, *Cancer cells assemble and align gold nanorods conjugated to antibodies to produce highly enhanced, sharp, and polarized surface Raman spectra: a potential cancer diagnostic marker*.

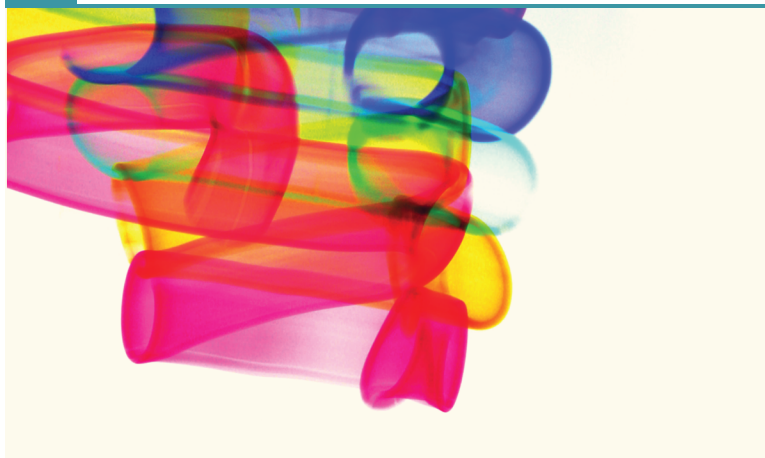
The work by Paras Prasad and colleagues is detailed in the paper, *Gold nanorods coated with multilayer polyelectrolyte as contrast agents for multimodal imaging*.

Source: Nano News - Gold Nanorods Image Tumors.

New Type of Nanoparticles

July 15, 2007.

Tags: Detection, Food, Laser, Nano-Oncology.



Luminiscent rings. Image: Tambako The Jaguar (CC BY-ND 2.0)

Researchers at UC Davis have created a new type of nanoparticles that could be used in tests for environmental pollution or contamination of food products, and for medical diagnostics.

The particles, about 100 to 200 nanometers in size, are luminescent, magnetic and inexpensive to make, and can be tagged with antibodies. They are made up of a magnetic core of iron oxide or iron/neodymium/cobalt oxide coated in a shell of europium and gadolinium oxide. When stimulated with a laser, europium emits red light at a very specific wavelength.

The nanoparticles can be manipulated with magnets and detected by fluorescence. They could also be labeled with other fluorescent labels in different colors, or used as part of an assay with other fluorescent labels. The built-in europium luminescence acts as an internal standard, making it easier to carry out accurate quantitative assays, said Ian Kennedy, professor of mechanical and aeronautical engineering and senior author on a paper describing the work.

The particles can also be coated with short pieces of DNA and used for genetic analysis. The team is exploring uses including testing for bioterrorism agents such as ricin or botulinum toxin in food and for genetic tests in cancer medicine.

The nanoparticles were made by spray pyrolysis, which involves mixing the raw material in a solvent and spraying it through a flame. The method is much cheaper than the techniques previously used for making similar particles, and can readily be scaled up to industrial production. It is already used in the chemical industry to make products such as fumed silica and carbon black...

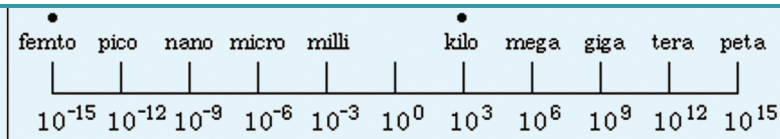
Source: Magnetic, Luminescent Nanoparticles Set New Standard.

Emergence of Femtomedicine

February 5, 2010.

Tags: Nanomedicine, Nano-Oncology.

Prefix	Symbol	Numerical	Exponential
yotta	Y	1,000,000,000,000,000,000,000,000	10^{24}
zetta	Z	1,000,000,000,000,000,000,000,000	10^{21}
exa	E	1,000,000,000,000,000,000,000	10^{18}
peta	P	1,000,000,000,000,000,000,000	10^{15}
tera	T	1,000,000,000,000,000,000,000	10^{12}
giga	G	1,000,000,000,000,000,000,000	10^9
mega	M	1,000,000,000,000,000,000,000	10^6
kilo	k	1,000,000,000,000,000,000,000	10^3
hecto	h	100,000,000,000,000,000,000	10^2
deca	da	10,000,000,000,000,000,000	10^1
no prefix means:		1	10^0
deci	d	0.1	10^{-1}
centi	c	0.01	10^{-2}
milli	m	0.001	10^{-3}
micro	μ	0.000 001	10^{-6}
nano	n	0.000 000 001	10^{-9}
pico	p	0.000 000 000 001	10^{-12}
femto	f	0.000 000 000 000 001	10^{-15}
atto	a	0.000 000 000 000 000 001	10^{-18}
zepto	z	0.000 000 000 000 000 000 001	10^{-21}
yocto	y	0.000 000 000 000 000 000 000 001	10^{-24}



quadrillionth

10⁻¹⁵

Femto- (symbol f) is a prefix in the metric system denoting a factor of 10^{-15} or 0.000000000000001.

Bombarding DNA nucleotides and mammalian meat with 'femto-neutrons' has opened up the path to femtomedicine, an entirely new cancer diagnostics, it was reported at First Global Congress on NanoEngineering for Medicine and Biology. **Femto-neutrons or 'femttons' are fast neutrons of femto-meter wavelength, a million times shorter than the current nanotechnology medical diagnostic probes that operate on nanometer scale.** In the first experiment of the kind, a collaboration of California Science & Engineering Corp. (CALSEC) and University of California, Irvine (UCI) College of Medicine, was able to detect oxygen differences as tiny as 1 atom of oxygen per molecule, one foot away, it is claimed. Since 'hypoxic' cancerous tumors contain 50% to 90% less oxygen than healthy tissue, if you find an oxygen difference between a tumor and the adjacent healthy tissue – you have diagnosed cancer! The principle is named 'Differential Femto Oximetry' or DFO, and the patented diagnostic probe 'Oncosensor'. "We are ready to test DFO in vivo using double blind animal trials at our center", said co-author Orhan Nalciglu, Professor and Director of the Center for Functional Onco Imaging of the UCI College of Medicine, which specializes in evaluation of diagnostic devices.

"Oncosensor's mission is to provide needleless biopsy with negligible 'false negatives' that is a quantum leap over the current technologies. It should facilitate an early warning, walk-in, painless, instant cancer diagnosis from outside the body, without intravenous fluid" - says Dr. Bogdan Maglich, CALSEC's Chief Technology Officer and the developer of the core technology that was originally used for defense, one of "50 Champions of Innovation" elected by Fast Company Magazine. The Oncosensor is not an imager. It will be used in tandem with any one of the imaging systems that have achieved very high sensitivity, almost 98%, in detecting tumors; but have a low 'specificity', about 70%, in differentiating healthy from malignant ones, thus missing an unacceptably large number of malignancies. CALSEC scientists predict Oncosensor's specificity will reach 98%, which is equal to or better than the surgical biopsy. This will be accomplished by making patients inhale 'carbogen', an oxygen enriched gas, the authors claim. Dr. Nisar Syed, Chancellor of American College of Radiation Oncology emphasized: "Oncosensor has the potential to significantly improve the eradication of malignant tumors by hyperthermia, the heat treatment by pointing to the least oxygenated tissue."

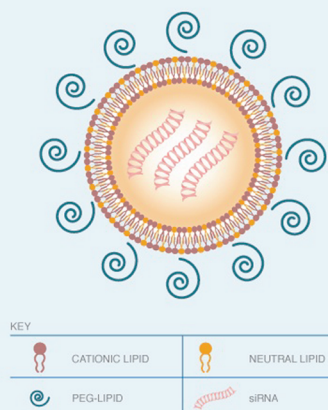
"The method has also the potential for the forewarning of stroke, Alzheimer's and cardiovascular diseases which, too, are marked by oxygen change," says co-author Dr. Anna Radovic, a molecular biologist.
Source: **Emergence of "Femtomedicine"- New Frontier of Biomed Sciences - Reported at First Global Congress on Nano Medicine.** More information in the presentation by Dr. Bogdan C. Maglich

First-in-Man Trial of RNAi Therapeutics Delivered with Lipid Nanoparticles

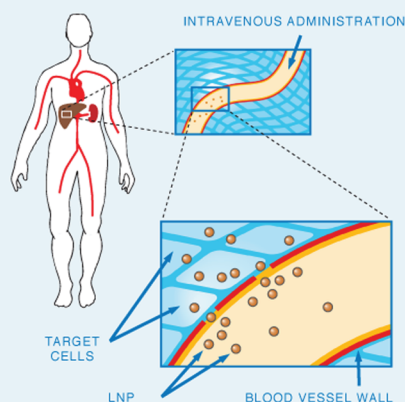
February 14, 2013.

Tags: Milestone, Nanomedicine, Drug Delivery, Nanoparticles, Nano-Oncology.

The LNP Particle



Nucleic Acid Delivery with LNP Technology



LNP technology relies on something called the enhanced permeability and retention effect, which occurs because these nucleic acid-containing particles have a long circulation time in the blood, resulting in increased accumulation at sites of vascular leak such as those found at sites of tumor cell growth, infection or inflammation. Once at the target site, cells take up the LNP through endocytosis and the nucleic acid payload is delivered inside the cell resulting in unparalleled potency. Credit: Tekmira Pharmaceuticals Corporation

tumors with liver involvement. Alnylam has licenses to Tekmira LNP intellectual property for use in RNAi therapeutic products using lipid nanoparticle (LNP) technology.

Source: Alnylam and Collaborators Publish Results from Phase I Clinical Trial and Extension Study with ALN-VSP, an RNAi Therapeutic for the Treatment of Liver Cancer

Significant results in treating cancer patients with nanoparticles containing ribonucleic acid interference (RNAi) molecules. This marks the first time that the therapeutic effect of RNAi has been demonstrated in humans.

A study led by Dr Josep Tabernero, the Director of Clinical Research at the Vall d'Hebron Institute of Oncology (VHIO) and Head of the Medical Oncology Department at the Vall d'Hebron University Hospital, shows for the first time that ribonucleic acid interference (RNAi) is effective in the treatment of cancer patients. Harnessing these molecules to silence genes involved in the development and growth of cancer cells is an important step forward in **developing a new and more targeted type of cancer therapy**. Dr Josep Tabernero, lead author of this study, said: "This is the first evidence to show that RNAi can be administered to cancer patients effectively, leading to significant tumour response."

In the new study, led by the Vall d'Hebron Institute of Oncology (VHIO), along with several other cancer research centres and the U.S. biotech company Alnylam, scientists have developed a lipid nanoparticle approach that can deliver two of RNAi molecules targeted against the genes encoding two key proteins involved in the development of cancer cells (VEGF and

KSP). This system takes the form of a novel drug (ALN-VSP) made up of RNAi molecules and lipid nanoparticles (LNPs).

Source: First-in-man study demonstrates the therapeutic effect of RNAi gene silencing in cancer treatment.

RNAi (RNA interference) is a revolution in biology, representing a breakthrough in understanding **how genes are turned on and off in cells, and a completely new approach to drug discovery and development**. Its discovery has been heralded as "a major scientific breakthrough that happens once every decade or so," and represents one of the most promising and rapidly advancing frontiers in biology and drug discovery today which was awarded the 2006 Nobel Prize for Physiology or Medicine. RNAi is a natural process of gene silencing that occurs in organisms ranging from plants to mammals. By harnessing the natural biological process of RNAi occurring in our cells, the creation of a major new class of medicines, known as RNAi therapeutics, is on the horizon. Alnylam is a biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi.

Alnylam has advanced its RNAi therapeutic, ALN-VSP, into the clinic for the treatment of liver cancers and potentially other solid

Tekmira believes its **lipid nanoparticle (LNP) technology represents the most widely adopted delivery technology for the systemic delivery of RNAi therapeutics**. Tekmira's LNP platform is being utilized in multiple clinical trials by both Tekmira and its partners. Tekmira's LNP technology (formerly referred to as stable nucleic acid-lipid particles or SNALP) encapsulates siRNAs with high efficiency in uniform lipid nanoparticles that are effective in delivering RNAi therapeutics to disease sites in numerous preclinical models.

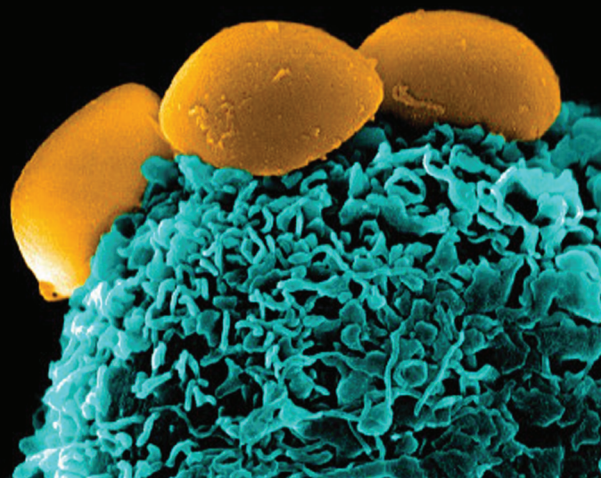
Source: Tekmira's LNP Technology Highlighted in Peer-Reviewed Publication, Cancer Discovery

This work is detailed in the paper "**First-in-Man Trial of an RNA Interference Therapeutic Targeting VEGF and KSP in Cancer Patients with Liver Involvement**" by Josep Tabernero, Geoffrey I. Shapiro, Patricia M. LoRusso, Andres Cervantes, Gary K. Schwartz, Glen J. Weiss, Luis Paz-Ares, Daniel C. Cho, Jeffrey R. Infante, Maria Alsina, Mrinal M. Gounder, Rick Falzone, Jamie Harrop, Amy C. Seila White, Iva Toudjarska, David Bumcrot, Rachel E. Meyers, Gregory Hinkle, Nenad Svrzikapa, Renta M. Hutabarat, Valerie A. Clausen, Jeff Cehelsky, Saraswathy V. Nochur, Christina Gamba-Vitalo, Akshay K. Vaishnav, Dinah W.Y. Sah, Jared A. Gollob and Howard A. Burris III.

First Drug-Carrying Nanoparticles that Look and Act like Cells

February 4, 2013.

Tags: Milestone, Nanomedicine, Drug Delivery, Nano-Oncology.



Camouflaged nanoparticles (yellow) cloaked in the membranes of white blood cells rest on the surface of an immune system cell (phagocyte, blue) without being recognized, ingested, and destroyed

By cloaking nanoparticles in the membranes of white blood cells, scientists at The Methodist Hospital Research Institute may have found a way to prevent the body from recognizing and destroying them before they deliver their drug payloads.

“Our goal was to make a particle that is camouflaged within our bodies and escapes the surveillance of the immune system to reach its target undiscovered,” said Department of Medicine Co-Chair Ennio Tasciotti, Ph.D., the study’s principal investigator. “We accomplished this with the lipids and proteins present on the membrane of the very same cells of the immune system. We transferred the cell membranes to the surfaces of the particles and the result is that the body now recognizes these particles as its own and does not readily remove them.”

Nanoparticles can deliver different types of drugs to specific cell types, for example, chemotherapy to cancer cells. But for all the benefits they offer and to get to where they need to go and deliver the needed drug, nanoparticles must somehow evade the body’s immune system that recognizes them as intruders. The ability of the body’s

defenses to destroy nanoparticles is a major barrier to the use of nanotechnology in medicine. **Systemically administered nanoparticles are captured and removed from the body within few minutes. With the membrane coating, they can survive for hours unharmed.**

“Our cloaking strategy prevents the binding of opsonins — signaling proteins that activate the immune system,” Tasciotti said. “We compared the absorption of proteins onto the surface of uncoated and coated particles to see how the particles might evade the immune system response.”

Tasciotti and his group took metabolically active leukocytes (white blood cells) and developed a procedure to separate membranes from cell innards. By coating their nanoparticles with intact membranes in their native composition of lipids and proteins, the researchers created the first drug-carrying nanoparticles that look and act like cells — **“LeukoLike Vectors”, or LLVs.**

“Using the membranes of white blood cells to coat a nanoparticle has never been done before,” Tasciotti said. “LLVs are half man-made — the synthetic silicon core — and

half made of man — the cell membrane.”

Source: Nanoparticles that look and act like cells. This work is detailed in the paper **“Synthetic nanoparticles functionalized with biomimetic leukocyte membranes possess cell-like function”** by Alessandro Parodi, Nicoletta Quattrocchi, Anne L. van de Ven, Ciro Chiappini, Michael Evangelopoulos, Jonathan O. Martinez, Brandon S. Brown, Sm Z. Khaled, Iman K. Yazdi, Maria Vittoria Enzo, Lucas Isenhardt, Mauro Ferrari & Ennio Tasciotti.

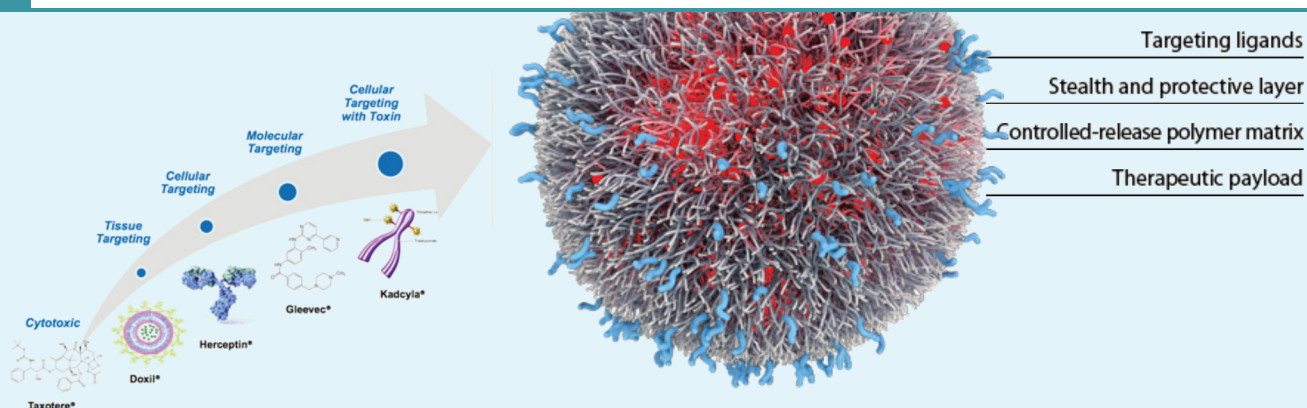
Context:

February 1, 2013. Nano World Cancer Day: How nanomedicine contributes to better cancer diagnostic and therapy

First Targeted and Programmable Nanomedicine to Show Clinical Anti-Tumor Effects

April 5, 2012.

Tags: Milestone, Nanomedicine, Nano-Oncology.



Accurins are polymeric nanoparticles that incorporate a therapeutic payload and are designed to have prolonged circulation within the bloodstream, enable targeting of the diseased tissue or cells, and provide for the controlled and timely release of the therapeutic payload. BIND's targeted Accurins consist of the following components that are optimized to achieve selective targeting of diseased cells and tissues. From BIND Therapeutics website (<http://bindtherapeutics.com>).

BIND Biosciences, a clinical-stage biopharmaceutical company developing a new class of highly selective targeted and programmable therapeutics called Accurins™, that are capable of up to a ten-fold increase in drug concentration at tumor sites, has published preclinical and clinical data showing promising effects in solid tumors and successful clinical translation of BIND-014, the first targeted and programmed nanomedicine to enter human clinical studies. In the paper BIND scientists describe BIND-014's ability to concentrate in tumors and provide preclinical and clinical data demonstrating efficacy, safety and pharmacological properties that are superior to and highly differentiated from the parent chemotherapeutic drug, docetaxel. BIND-014 is the first clinical-stage targeted therapeutic nanoparticle with programmable pharmacological properties, including particle circulation time, pharmacokinetic profile, biodistribution and release profile. BIND-014 has been shown to effectively target a receptor expressed in tumors to achieve high drug concentrations at the site of disease.

"These seminal data on BIND's first clinical stage Accurin, BIND-014, demonstrates for the first time that it is possible to generate medicines with both targeted

and programmable properties that can concentrate the therapeutic effect directly at the site of disease, potentially revolutionizing how complex diseases such as cancer are treated," commented Omid Farokhzad, M.D, BIND Founder and Associate Professor, Harvard Medical School. "BIND's data are a giant leap forward in achieving the true promise of nanomedicine by enabling the design of therapeutics with highly-differentiated efficacy and safety that go above and beyond the capabilities of traditional drug design through medicinal chemistry."

"Previous attempts to develop targeted nanoparticles have not translated into clinical success because of the inherent difficulty of designing and scaling up a particle capable of targeting, long-circulation via immune-response evasion, and controlled drug release," commented Robert Langer, Sc.D., BIND Founder and David H. Koch Institute Professor at MIT.

BIND-014 is **the first therapeutic of its kind to reach clinical evaluation and has demonstrated an increases of up to ten fold in drug concentration in tumors, which lead to substantially better efficacy and safety.** This represents a major advance in cancer therapy and a

significant milestone for science, technology and medicine.

Study coauthors included scientific and clinical advisors from the Massachusetts Institute of Technology (MIT), Harvard Medical School and Dana-Farber Cancer Institute, Weill Cornell Medical College, the Translational Genomics Research Institute (TGen), Karmanos Cancer Institute and Wayne State University.

Source: BIND Biosciences Publishes Data on BIND-014, the First Targeted and Programmable Nanomedicine to Show Clinical Anti-Tumor Effects. This work is detailed in the paper "**Preclinical Development and Clinical Translation of a PSMA-Targeted Docetaxel Nanoparticle with a Differentiated Pharmacological Profile**"

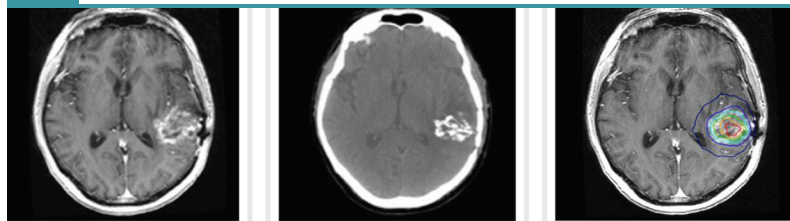
Context:

November, 2011. A realistic look at the promises and perils of nanomedicine July 2011. First synthetic organ transplant July 2010. World's first nanoparticle-based cancer treatment to come to market December 2008. Nano in Onco, getting closer by Victor Puentes

World's First Nanoparticle-Based Cancer Treatment to Come to Market

July 8, 2010.

Tags: Milestone, Nanomedicine, Nano-Oncology, Nanoparticles.



INJECTION OF NANOTHERM® NANOPARTICLES

IN A PROCEDURE SIMILAR TO A BIOPSY, NANOPARTICLES ARE INJECTED AND DISTRIBUTED WITHIN TUMOR.

Fighting Cancer with Nanomedicine.

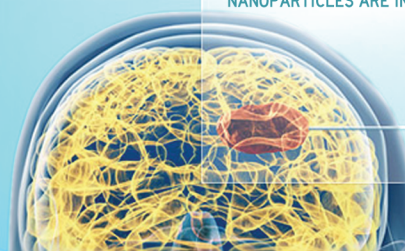


Image composition from MagForce website (<http://www.magforce.de>).

Following more than 20 years of research and development efforts, MagForce Nanotechnologies AG, a majority-owned subsidiary of Nanostart AG, **has received regulatory approval for medical use of its Nano-Cancer® therapy throughout the European Union.** This momentous event marks the world's first nanoparticle-based cancer treatment to come to market.

Approval was granted for the treatment of brain tumors.

This novel therapy involves the instillation directly into the tumor of a fluid containing special iron oxide nanoparticles. These magnetic nanoparticles are then subjected to a controlled magnetic field so that they oscillate and generate heat. The elevated temperature within the tumor causes the cancer cells to be damaged or destroyed.

This approval follows successful completion of the conformity evaluation procedure of the company's NanoTherm® magnetic fluid by Medcert GmbH and of its NanoActivator® magnetic field applicator by Berlin Cert GmbH. Both of these medical certification and testing companies are officially authorized centers for the

conformity evaluation of medical devices.

"With regulatory approval now received, our company has entered a new phase. MagForce is transforming itself from a medical R&D company to a commercial provider of medical technology," said Dr. Peter Heinrich, CEO of MagForce Nanotechnologies.

MagForce founder and CSO Dr. Andreas Jordan added, "After research and development efforts spanning more than 20 years, we now have regulatory approval in hand. This is a historic moment for us."

This regulatory approval gives the green light for the company to proceed with its planned market launch of Nano-Cancer® therapy, which will commence in the coming weeks.

Nanostart CEO Marco Beckmann underscored that "regulatory approval was granted not just for glioblastoma but for the treatment of all brain tumors, thus opening enormous market potential for the new therapy. We congratulate the management team and entire staff at MagForce on this tremendous success."

The regulatory approval was received based on the results of a clinical study in patients

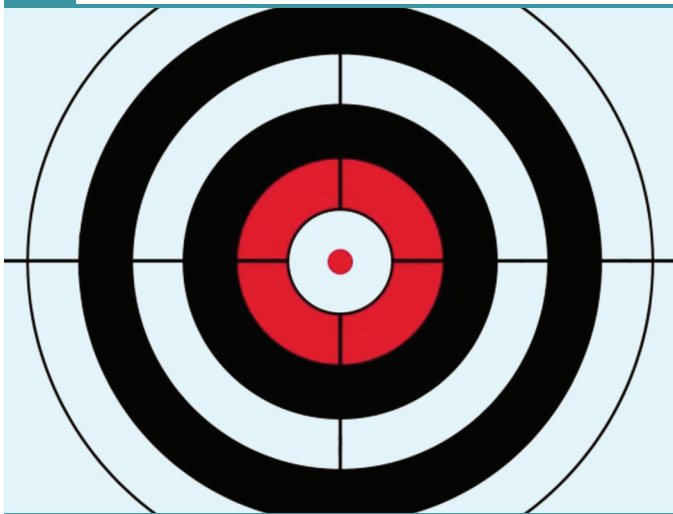
suffering from recurrent glioblastoma, a particularly aggressive and deadly form of brain tumor. In these clinical trials, the new therapy was able to demonstrate its remarkable effectiveness, with median patient survival time increased from 6.2 months using conventional therapies to 13.4 months using Nano-Cancer® therapy in combination with radiotherapy. **Median patient survival following diagnosis of the recurrence was thus more than doubled. Furthermore, compared to existing conventional treatments, the side effects and patient discomfort associated with the new therapy are minimal.**

Source: Nanostart subsidiary MagForce Nanotechnologies receives EU regulatory approval for its Nano-Cancer® therapy

Nanotechnology to Localize and Control Drug Delivery

February 10, 2008.

Tags: Nanomedicine, Drug Delivery, Nano-Oncology, Nanomaterial.



Using nanotechnology, scientists from UCLA and Northwestern University have developed a localized and controlled drug delivery method that is invisible to the immune system, a discovery that could provide newer and more effective treatments for cancer and other diseases. The study provides an example of the enormous potential and clinical significance that nanomaterials may represent in such fields as oncology, endocrinology and cardiology.

The researchers used nanoscale polymer films, about four nanometers per layer, to build a sort of matrix or platform to hold and slowly release an anti-inflammatory drug.

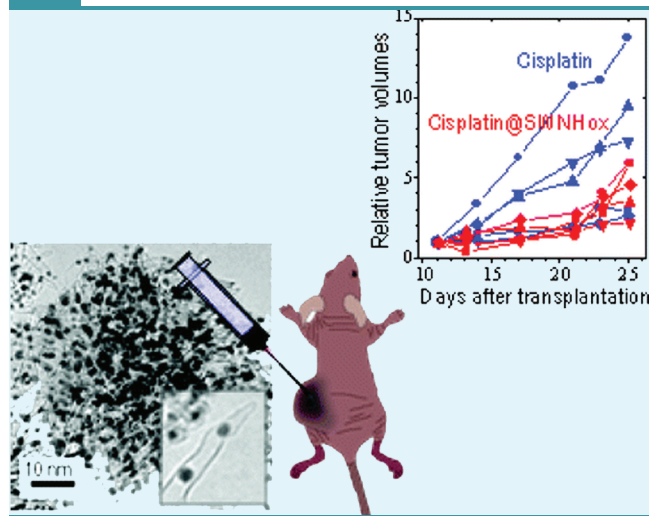
The nanomaterial technology serves as a non-invasive and biocompatible platform for the delivery of a broad range of therapeutics. The technology also may prove to be an effective approach for delivering multiple drugs, controlling the sequence of multi-drug delivery strategies and enhancing the life spans of commonly implanted devices such as cardiac stents, pacemakers and continuous glucose monitors. "For chemotherapy, this system could enhance treatment efficacy while preventing uncontrolled delivery and the resultant patient side effects."

Source: Scientists use nanotechnology to localize and control drug delivery

Enhancement of In Vivo Anticancer Effects of Cisplatin

Victor Puentes. October 9, 2008.

Tags: Nanomedicine, Drug Delivery, Nano-Onc.



Another set of experiments show the promise of nanoparticles and carbon nanostructures as efficient vehicles for cancer treatment. Cisplatin was incorporated inside single-wall carbon nanohorns with holes opened by a nanoprecipitation method that involved dispersion of cisplatin and the nanostructures in a solvent followed by the solvent evaporation. The incorporated cisplatin quantity increased from the previously reported value of 15 to 46%, and the total released quantity of cisplatin also increased from 60 to 100% by changing the solvent from dimethylformamide to water. Concurrently, in vitro anticancer efficiency increased to 46 times greater than that of the free cisplatin.

In vivo, cisplatin vehiculized by the carbon nanohorn intratumorally injected to transplanted tumors of mice suppressed the tumor growth more than the intact cisplatin. Adhesion of the nanostructure to the cell surfaces in vitro and within the tumor tissues in vivo is probably the key in the observed effects.

However, the carbon nanohorns show also cytotoxicity, what may on one side increase the toxicity of the conjugated drug but also result in undesired toxic side effects due to the inherent toxicity of carbon nanotubes, fullerenes and their derivatives.

Source: Enhancement of In Vivo Anticancer Effects of Cisplatin by Incorporation Inside Single-Wall Carbon Nanohorns by Kumiko Ajima, Tatsuya Murakami, Yoshikazu Mizoguchi, Kunihiro Tsuchida, Toshinari Ichihashi, Sumio Iijima, and Masako Yudasaka.

See also: Cisplatin and Carbon Nanotubes [Next page].

Cisplatin and Carbon Nanotubes

Victor Puentes. July 12, 2008.

Tags: Nanomedicine, Nano-Oncology, Carbon Nanotubes, Drug Delivery.

Antineoplastic effects of Cisplatin, a paradigm of serendipity, were discovered when applying electric fields to *C. Elegans*. In that case, the Pt(II) cations released from the electrodes interfered with cellular duplication and the *C. Elegans* grew to gigantic sizes. First was thought that the applied electrical induced organism growth however later on was found that Cisplatin irreversibly attaches to the N residues of the DNA impeding cell reproduction. Since then it has been one of the most used antitumoral drugs and still today is widely used in the treatment of the most prevalent tumours. In addition, Cisplatin derivatives as carboplatin or oxiplatin has show also beneficial therapeutic effects, indicating

that modifications of cisplatin may be of medical interest. Therefore many compounds based on Pt(II) has been produced showing biological activity, however, few of them have shown medical relevance. The loose of activity in the body can be associated with deactivation of the Pt(II) cation by sulfure containing molecules (cisteines) or by a unproper biodistribution of the drug, and others. In a recent paper, Lippard and co-workers have try to overcome this complications by conjugating platine(IV) compounds to carbon nanotubes. The carbon nanotubes should act as Longboat Delivery Systems for Platinum (IV). Such nanocomposites are internalized by endocytosis into a endosome where its low pH reduces

Platinum (IV) to Platinum (II) delivering a large amount of cisplatin(II) to the cell increasing efficiently its killer effects. In addition, circulating Platinum (IV) compounds are non toxic (it is the valence II compound the toxic one). Now it has to be observed the compound biodistribution and side effects since generally platinum chemotherapies are interrupted due to size effects of nefro toxicity or renal toxicity.

Source: Feazell et al. *Journal of the American Chemical Society* 2007, 129,8438-8439

Researchers' Nanotube Findings Give Boost to Potential Biomedical Applications

February 10, 2008.

Tags: Nanomedicine, Carbon Nanotubes, Nanotoxicology, Drug Delivery, Concerns, Nano-Oncology

A team of scientists at Stanford University has tracked the movement of carbon nanotubes through the digestive systems of mice. They've determined that the nanotubes do not exhibit any toxicity in the mice, and are safely expelled after delivering their payload. As a result, the study paves the way toward future applications of nanotubes in the treatment of illnesses. Previous research by the same team demonstrated that nanotubes can be used to fight cancer. The nanotubes do this in two ways. One method involves shining laser light on the nanotubes, which generates heat to destroy cancer cells. Another method involves attaching medicine to the nanotubes, which are able to accurately 'find' cancerous cells without impacting healthy cells.

Source: **Researchers' nanotube findings give boost to potential biomedical applications**

First Direct Images of Carbon Nanotubes Entering Cells

November 26, 2007.

Tags: Carbon Nanotubes, Nanotoxicology, Concerns.



This transmission electron microscope image shows carbon nanotubes (dark areas) within a cell nucleus.

For the first time, scientists have directly imaged carbon nanotubes entering and migrating within human cells, determining as a result that whether the nanotubes cause cell death depends on the dose and exposure time.

Source: **First Direct Images of Carbon Nanotubes Entering Cells**

Nanotube-Producing Bacteria

December 13, 2007.

Tags: Nanobiotechnology, Carbon Nanotubes, Nanoelectronics, Nano Before Nanotech.



Shewanella bacteria (shown in blue) forming nanotubes

Engineers at the University of California, Riverside are part of a team that has found semiconducting nanotubes produced by living bacteria – a discovery that could help in the creation of a new generation of nanoelectronic devices.

The research team believes this is the first time nanotubes have been shown to be produced by biological rather than chemical means. It opens the door to the possibility of cheaper and more environmentally friendly manufacture of electronic materials.

Shewanella bacteria (shown in blue) forming nanotubes

The team found the bacterium *Shewanella* facilitates the formation of arsenic-sulfide nanotubes that have unique physical and chemical properties not produced by chemical agents. The photoactive arsenic-sulfide nanotubes produced by the bacteria behave as metals with electrical and photoconductive properties. The researchers report that these properties may also provide novel functionality for the next generation of semiconductors in nano- and opto-electronic devices. In a process that is not yet fully understood, the *Shewanella* bacterium secretes polysaccharides that seem to produce the template for the arsenic sulfide nanotubes,

Source: Nanotube-producing Bacteria Show Manufacturing Promise

JPL Nanotubes Help Advance Brain Tumor Research

January 17, 2008.

Tags: Drug Delivery, Nanomedicine, Nano-Oncology.



Benham Badie, M.D., director of the Department of Neurosurgery and the Brain Tumor program at City of Hope, performs a minimally invasive procedure to surgically remove a pituitary tumor. Nanotube technology may help in the development of new treatments that would require only minimally invasive procedures no matter the location of the brain tumor. Image credit: City of Hope

The potential of carbon nanotubes to diagnose and treat brain tumors is being explored through a partnership between NASA's Jet Propulsion Laboratory, Pasadena, Calif., and City of Hope, a leading cancer research and treatment center in Duarte, Calif.

Nanotechnology may help revolutionize medicine in the future with its promise to play a role in selective cancer therapy. City of Hope researchers hope to boost the brain's own immune response against tumors by delivering cancer-fighting agents via nanotubes.

If nanotube technology can be effectively applied to brain tumors, it might also be used to treat stroke, trauma, neurodegenerative disorders and other disease processes in the brain, said Dr. Behnam Badie, City of Hope's director of neurosurgery and of its brain tumor program.

The Nano and Micro Systems Group at JPL, which has been researching nanotubes since about 2000, creates these tiny, cylindrical multi-walled carbon tubes for City of Hope. (See [nasa nanotechnology comes to market](#))

City of Hope researchers, who began their quest in 2006, found good results: The nanotubes, which they used on mice, were non-toxic in brain cells, did not change cell reproduction and were capable of carrying DNA and siRNA, two types of molecules that encode genetic information.

JPL's Nano and Micro Systems Group grows the nanotubes on silicon strips a few square millimeters in area. The growth process forms them into hollow tubes as if by rolling sheets of graphite-like carbon.

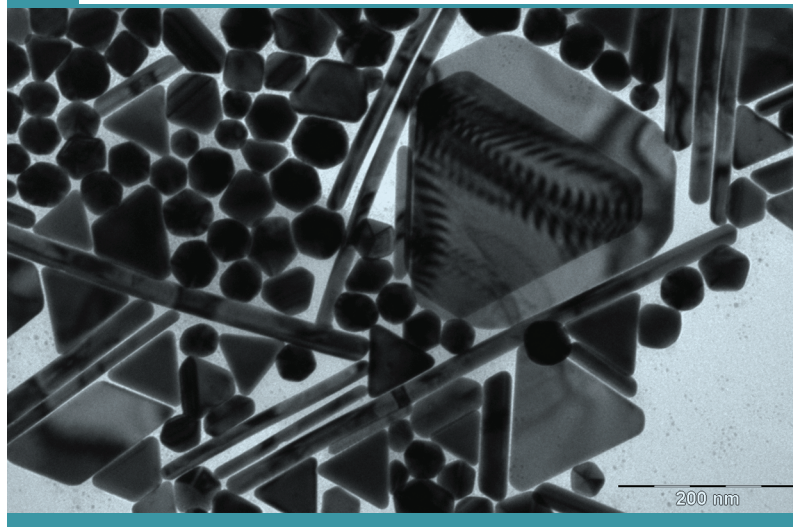
Carbon nanotubes are extremely strong, flexible, heat-resistant, and have very sharp tips. Consequently, JPL uses nanotubes as field-emission cathodes — vehicles that help produce electrons — for various space applications such as x-ray and mass spectroscopy instruments, vacuum microelectronics and high-frequency communications. (See [nano-detector very promising for remote cosmic realms](#)).

Source: JPL Nanotubes Help Advance Brain Tumor Research

Gold Nanoparticles: a Potential Platform for Target- Specific Therapies in Cancer

Marc Ramis. July 8, 2008.

Tags: Nanomedicine, Nano-Oncology, Nanoparticles.



MV-50 (30 uL Pt seeds) 1 day
Image by Victor Puentes.

Gold Nanoparticles were strongly supported as a drug-payload delivery system during 2008 NSTI meeting celebrated in Boston this June.

Dr. Piotr Grodzinski is Director of Nanotechnology for Cancer programs at Nanotechnology Alliance of National Cancer Institute (NCI) in Bethesda, Maryland. The NCI, part of the National Institutes of Health, is engaged in efforts to harness the power of nanotechnology to radically change the way we diagnose, treat and prevent cancer.

In his keynote lecture "Clinical translation of Nanotechnology for Cancer: The NCI Alliance's Perspective", he reviewed the most relevant NCI current initiatives and Gold Nanoparticles applications were introduced as a major area of focus:

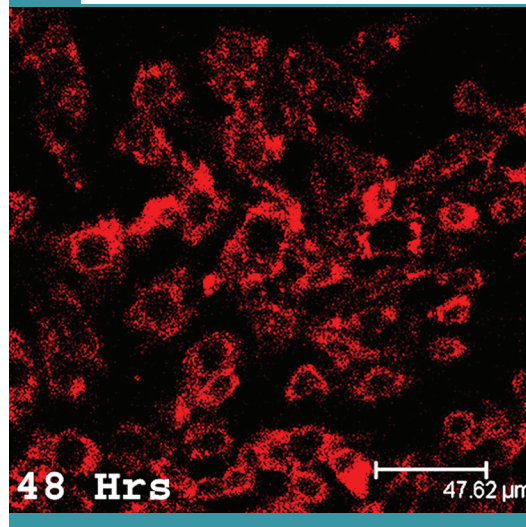
For example, Dr. Grodzinski introduced CytImmune's lead drug candidate. Aurimmune consists of recombinant human tumor necrosis factor alpha (a known tumor-killing agent) bound to the surface of Gold Nanoparticles (Phase I).

Also, Dr. Grodzinski presented AuroLase Cancer Therapy, a novel cancer treatment that combines the unique physical and optical properties of Gold Nanoparticles with a near infrared laser source to thermally destroy cancer cells without significant damage to surrounding tissue. This technology is developed by Nanospectra Bioscience and FDA just approved to commence a human trial in patients with head and neck cancer.

This Drug Delivers Itself

July 15, 2007.

Tags: Nanomedicine, Nano-Oncology, Drug Delivery.



This confocal microscope image shows uptake of the nanocrystals by cancer cells, a technique developed by researchers at UB and RPCI.

The problem of efficiently delivering drugs, especially those that are hydrophobic or water-repellant, to tumors or other disease sites has long challenged scientists to develop innovative delivery systems that keep these drugs intact until reaching their targets.

Now scientists in the University at Buffalo's Institute for Lasers, Photonics and Biophotonics and Roswell Park Cancer Institute have developed an innovative solution in which the delivery system is the drug itself.

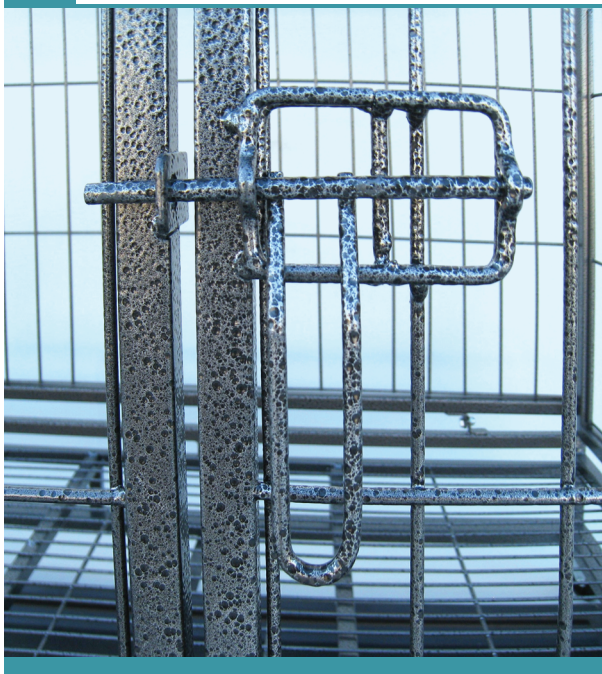
They describe for the first time in Molecular Pharmaceutics a drug delivery system that consists of nanocrystals of a hydrophobic drug.

Source: No Carrier Necessary: This Drug Delivers Itself - UB NewsCenter

Cage Nanoparticles vs Cancer

July 15, 2007.

Tags: Nanomedicine, Nano-Oncology, Drug Delivery, Implant.



Researchers at Montana State University have used an engineered form of ferritin, a cage-like iron storage protein, to both synthesize and deliver iron oxide nanoparticles to tumors. The investigators, led by Trevor Douglas, Ph.D., and Mark Young, Ph.D., reported their findings in the *Journal of the American Chemical Society*.

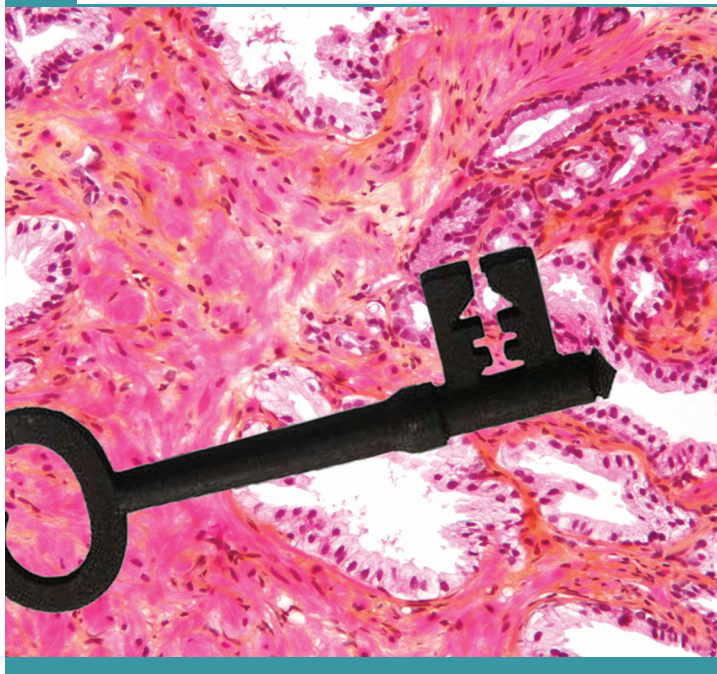
The researchers note that the use of other cage-like proteins, instead of ferritin, could provide a wide range of tools for targeting tumors and delivering imaging agents and drugs to malignant cells.

Source: Targeting of cancer cells with ferrimagnetic ferritin cage nanoparticles

'Passkey' into Cancer

July 15, 2007.

Tags: Nanomedicine, Nano-Oncology, Drug Delivery.



Scientists at Rice University and Baylor College of Medicine have discovered a new way to use Rice's famed buckyball nanoparticles as passkeys that allows drugs to enter cancer cells.

The passkeys that Barron and colleagues developed contain a molecule called Bucky amino acid that was created in Barron's lab. Bucky amino acid, or Baa, is based on pheyalanine, one of the 20 essential amino acids that are strung together like beads on a necklace to build all proteins.

Barron's graduate student, Jianzhong Yang, developed several different Baa-containing peptides, or slivers of protein containing about a dozen or so amino acids. In their natural form, with pheyalanine as a link in their chain, these peptides did not pass through the cell walls.

Barron's group collaborated with Yang's brother, Baylor College of Medicine assistant professor Jianhua Yang at Texas Children's Cancer Center, and found the Baa-containing peptides could mimic viral proteins and pass through the walls of cancer cells. The peptides were found effective at penetrating the defenses of both liver cancer cells and neuroblastoma cells.

Source: Buckyballs used as 'passkey' into cancer cells

Nano Drug Crosses Blood-Brain Tumor Barrier

July 22, 2013.

Tags: Nano-Oncology. Nanomedicine.



The Blood Brain Barrier and Astrocytes type 1. Author: Ben Brahim Mohammed. Source: Wikimedia Commons.

An experimental drug in early development for aggressive brain tumors can cross the blood-brain tumor barrier, kill tumor cells and block the growth of tumor blood vessels, according to a study led by researchers at the Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James).

The laboratory and animal study also shows how the agent, called SapC-DOPS, targets tumor cells and blood vessels. The findings support further development of the drug as a novel treatment for brain tumors.

Glioblastoma multiforme is the most common and aggressive form of brain cancer, with a median survival of about 15 months. A major obstacle to improving treatment for the 3,470 cases of the disease expected in the United States this year is the blood-brain barrier, the name given to the tight fit of cells that make up the blood vessels in the brain. That barrier protects the

brain from toxins in the blood but also keeps drugs in the bloodstream from reaching brain tumors.

“Few drugs have the capacity to cross the tumor blood-brain barrier and specifically target tumor cells,” says principal investigator Balveen Kaur, PhD, associate professor of neurological surgery and chief of the Dardinger Laboratory of Neurosciences at the OSUCCC – James. “Our preclinical study indicates that SapC-DOPS does both and inhibits the growth of new tumor blood vessels, suggesting that this agent could one day be an important treatment for glioblastoma and other solid tumors.”

SapC-DOPS (saposin-C dioleoylphosphatidylserine), is a nanovesicle drug that has shown activity in glioblastoma, pancreatic cancer and other solid tumors in preclinical studies. The nanovesicles fuse with tumor cells, causing them to self-destruct by apoptosis.

Source: Nano Drug Crosses Blood-Brain Tumor Barrier, Targets Brain Tumor Cells and Blood Vessels. This work is detailed in the paper “**Systemic Delivery of SapC-DOPS Has Antiangiogenic and Antitumor Effects Against Glioblastoma**” by Jeffrey Wojton, Zhengtao Chu, Haritha Mathsyaraja, Walter H Meisen, Nicholas Denton, Chang-Hyuk Kwon, Lionel ML Chow, Mary Palascak, Robert Franco, Tristan Bourdeau, Sherry Thornton, Michael C Ostrowski, Balveen Kaur and Xiaoyang Qi.

Context:

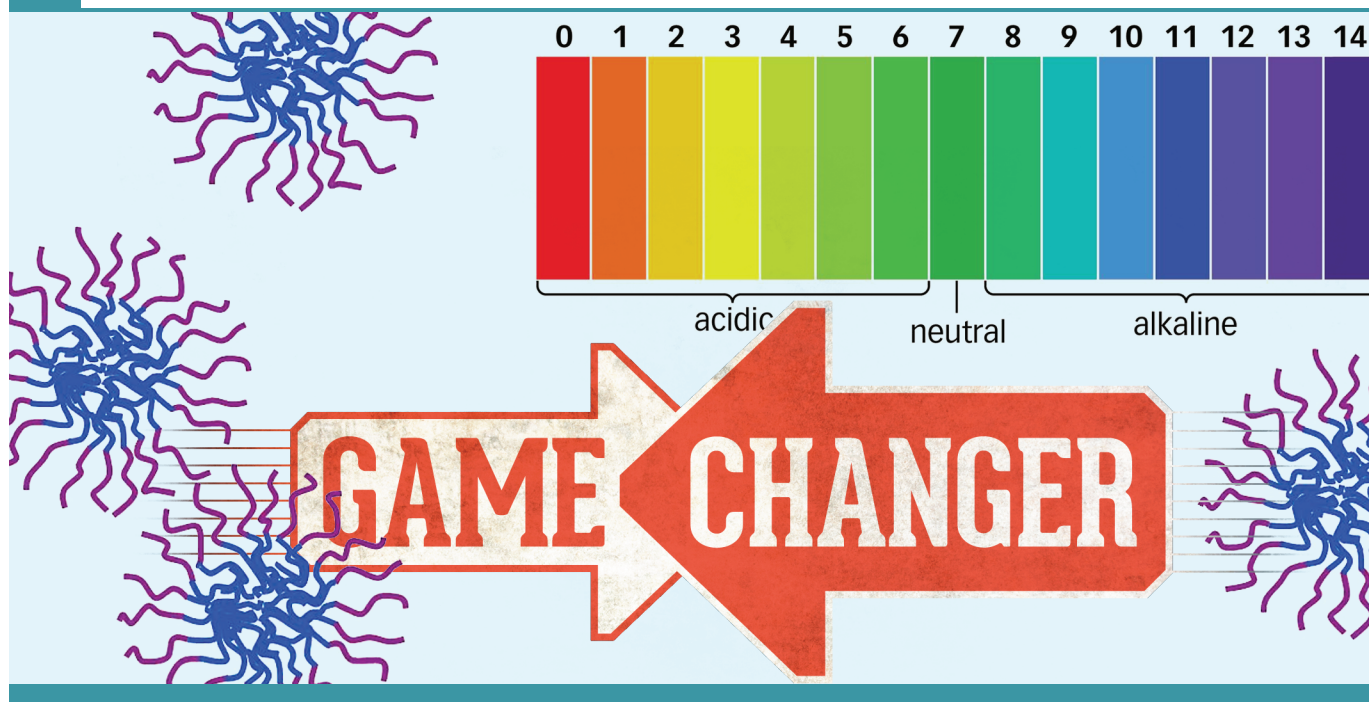
April 19, 2013. Delivering life-saving drugs to the brain

July 8, 2010. World's first nanoparticle-based cancer treatment to come to market November 3, 2009. Final clinical trials for Nano-Cancer® therapy May 14, 2009. Diagnosis through breath January 17, 2008. JPL Nanotubes Help Advance Brain Tumor Research

Nanoparticles, 'pH phoresis' Could Improve Cancer Drug Delivery

July 12, 2013.

Tags: Nanobiotechnology, Nanoparticles, Drug Delivery, Nano-Oncology, Nanomedicine.



Researchers have developed a concept to potentially **improve delivery of drugs for cancer treatment using nanoparticles that concentrate and expand in the presence of higher acidity found in tumor cells.**

The concept involves using nanoparticles made of "weak polybases," compounds that expand when transported into environments mimicking tumor cells, which have a higher acidity than surrounding tissues. The researchers used sophisticated modeling to show how the particles would accumulate in regions of higher acidity and remain there long enough to deliver anticancer drugs.

"This phenomenon, which we term pH phoresis, may provide a useful mechanism for improving the delivery of drugs to cancer cells in solid tumor tissues," said You-Yeon Won, an associate professor of chemical engineering at Purdue University.

Solutions with a pH less than 7 are said

to be acidic, and those with a higher pH are basic or alkaline. The pH phoresis concept hinges on using synthetic "polymer micelles," tiny drug-delivery spheres that harbor medications in their inner core and contain an outer shell made of a material that has been shown to expand dramatically as the pH changes from alkaline to acidic.

A twofold size increase could result in a similar increase in the efficiency of drug delivery to tumors.

"Such an effect would be a game changer by delivering the proper dose of anticancer drugs inside tumor cells," Won said.

"This pH phoresis concept also could be combined readily within other established drug-delivery methodologies, making it potentially practical for medical application."

More research is needed to determine how well the approach could enhance drug delivery, but the pH phoresis concept developed by Won and his

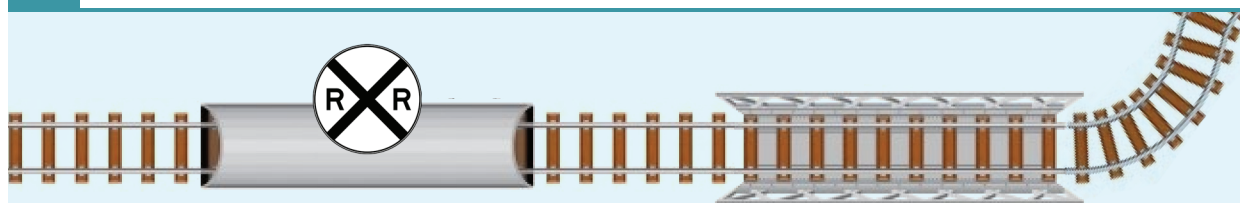
student represents a step in developing nanomedicine techniques in drug delivery, he said.

Source: Nanoparticles, 'pH phoresis' could improve cancer drug delivery by Emil Venere. This work is detailed in the paper **"pH phoresis": A new concept that can be used for improving drug delivery to tumor cells** by You-Yeon Won, Hoyoung Lee.

'Nanotrain' for Targeted Cancer Drug Transport

May 1, 2013.

Tags: Drug Delivery, DNA Nanotechnology, Nanomedicine, Nano-Oncology.



Researchers have developed a "DNA nanotrain" that fast-tracks its payload of cancer-fighting drugs and bioimaging agents to tumor cells deep within the body. The nanotrain's ability to cost-effectively deliver high doses of drugs to precisely targeted cancers and other medical maladies without leaving behind toxic nano-clutter has been the elusive Holy Grail for scientists studying the teeny-tiny world of DNA nanotechnology.

DNA nanotechnology holds great promise as a new way to deliver chemotherapy directly to cancer cells, but until now, scientists have not been able to direct nanotherapies to consistently differentiate cancer cells from healthy ones. Other limiting factors include high costs, too-small amounts of drugs delivered and potential toxic side effects.

"Most nanotechnology relies on a nanoparticle approach, and the particles are made of inorganic materials; after they've been used as a carrier for the drug, they'll be left inside the body," said the study's lead investigator, Weihong Tan, a UF distinguished professor of chemistry, professor of physiology and functional genomics, and a member of the UF Shands Cancer Center and the UF Genetics Institute. "Compared to existing nanostructures, our nanotrain is easier and cheaper to make, is highly specific to cancer cells, has a lot of drug-loading power and is very much biocompatible."

Tan's DNA nanotrain is a three-dimensional structure composed of short strands of DNA tethered together into one long train. On the end of the nanotrain is an aptamer, a tiny piece of nucleic acid serving as the train's "locomotive" on biochemical autopilot to home in on and bind to specific cancer cells. Trailing behind are tethered DNA structures that serve as side-by-side, high-capacity "box cars,"

transporting bioimaging agents or drug cargos to their targets.

"The beauty of the nanotrain is that by using different disease biomarkers you can hitch different types of DNA probes as the train's 'locomotive' to recognize and target different types of cancers," Tan said. "We've precisely targeted leukemia, lung and liver cancer cells, and because the DNA probes are so precise in targeting only specific types of cancer cells we've seen dramatic reduction in drug toxicity in comparison to standard chemotherapies, which don't discriminate well between cancerous and healthy cells."

Tan and his colleagues report that the DNA nanotrains can be cost-effectively made by mixing bits of DNA in a liquid medium. The mixture is then exposed to a compound that stimulates the pieces of DNA to seek each other out and self-assemble into the DNA nanotrains. The type of cancer cell the DNA nanotrain will seek out and destroy is determined by the specific compound added to the mixture as the trigger.

The study demonstrated in vitro and in mice that the DNA nanotrains exclusively target the cancer cells for which their probes were programmed. The DNA probes go straight to the cancer cells, leading the nanotrains to dock on the cell membranes and gain entry into the cells. Once inside, the drug payloads disperse, killing the cancer cells, a process Tan and his team monitored in real time by measuring the amount of fluorescent light emitted. The biodegradable components of the DNA nanotrains decay with the dead cancer cells and are removed by the body's normal housekeeping mechanisms.

"Our study found that when loaded with anticancer drugs, these nanotrains inhibited

tumor growth in mice more than in those that received drugs injected freely into the bloodstream. What's more exciting is that the mice treated with these nanotrains suffered dramatically fewer side effects than those treated with free drugs," said Guizhi Zhu, a UF doctoral student who was instrumental in the study. "This is what we aim to achieve for future clinical health care of cancer patients."

In addition to longer survival and inhibited tumor growth, the mice that were treated with nanotrain drug delivery experienced less weight loss and are in better condition physically than both the mice that received injected therapy and the mouse control group that received no treatment. Tan and his team attribute these improved outcomes to greatly reduced toxicity achieved by the targeted nanotrain drug delivery.

"We think we have demonstrated that these DNA nanotrains are a promising targeted drug transport platform for delivery of cancer chemotherapeutics with very low toxicity to healthy tissues, and that the platform has wide application for many different cancer types," Tan said. "Moving forward, we are working to identify optimum dosage using mouse models for T-cell leukemia, lung and liver cancers and triple negative breast cancer."

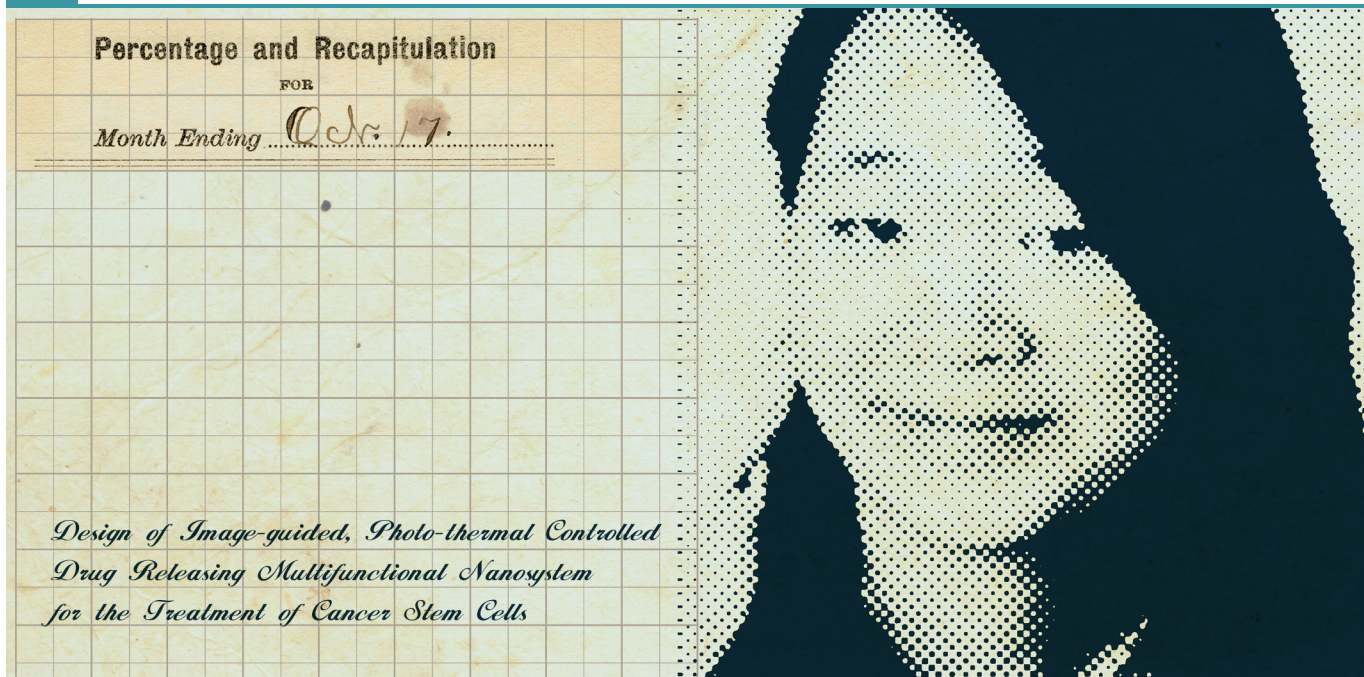
"It's very exciting, but we still have a long way to go before human trials," he said.

Source: UF researchers develop 'nanotrain' for targeted cancer drug transport. This work is detailed in the paper **"Self-assembled, aptamer-tethered DNA nanotrains for targeted transport of molecular drugs in cancer theranostics"** by Guizhi Zhua, Jing Zheng, Erqun Song, Michael Donovan, Kejing Zhang, Chen Liu, and Weihong Tan.

17-Year-Old Wins 100k \$ for Creating Cancer-Killing Nanoparticle

December 12, 2011.

Tags: Nanoparticles, Nanomedicine, Nano-Oncology, Educational.



Angela Zhang, 17-year-old wins 100k for creating cancer-killing nanoparticle

Siemens Foundation announced winners of the Siemens Competition in Math, Science & Technology, "revealing the brightest high school minds in contention for the nation's most coveted teen science prize." The Siemens Competition in Math, Science & Technology recognizes remarkable talent early on, fostering individual growth for high school students who are willing to challenge themselves through science research. Through this competition, students have an opportunity to achieve national recognition for science research projects that they complete in high school.

Design of Image-guided, Photo-thermal Controlled Drug Releasing Multifunctional Nanosystem for the Treatment of Cancer Stem Cells - Biochemistry

MENTOR: Dr. Zhen Cheng, Stanford University

"I was surprised by the survival rate of

patients who had undergone current cancer therapy."

Cancer stem cells (CSCs) are responsible for initiating and driving tumor growth yet are often resistant to current cancer therapies. In her research, Angela Zhang aimed to design a CSC-targeted, gold and iron oxide-based nanoparticle with a potential to eradicate these cells through a controlled delivery of the drug salinomycin to the site of the tumor. The multifunctional nanoparticle combines therapy and imaging into a single platform, with the gold and iron-oxide components allowing for both MRI and Photoacoustic imaging. This nanosystem could potentially help overcome cancer resistance, minimize undesirable side effects, and allow for real-time monitoring of treatment efficacy.

Angela, a senior, is interested in nanomedicine and molecular imaging because they allow her "to transform my interests in physics, chemistry, and biology

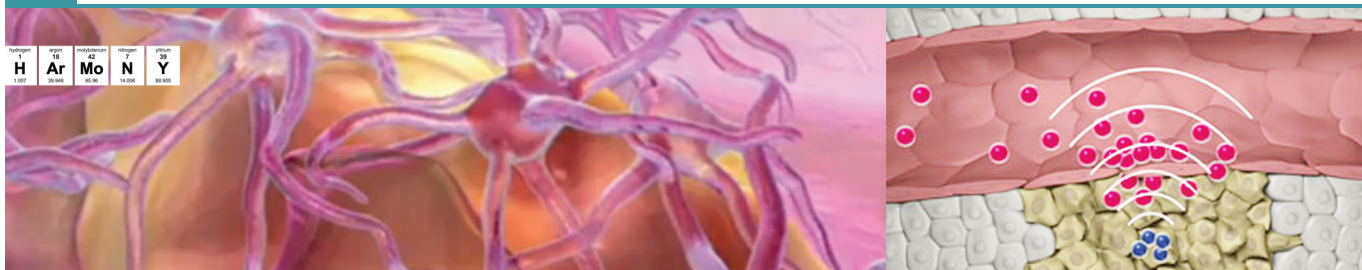
into solutions for current health problems." She won the Intel International Science & Engineering Fair (ISEF) 2011 Grand Award and the ISEF 2010 Grand Award (both for medicine and health science), and a trip to attend the Taiwan International Science Fair awarded by the National Taiwan Science Education Center. Angela planned and executed a fundraiser that raised over \$5,000 a year for the Monta Vista Interact International Night and has participated in the Jade Ribbon Youth Council to raise awareness about Hepatitis B. She plays golf and the piano and would like to major in chemical or biomedical engineering or physics. She was a 2010 Siemens Competition Regional Finalist who put in 1,000 hours on her current project. Angela hopes to become a research professor.

Source: **2011 Siemens Competition in Math, Science & Technology**

Nanoparticles Communicate with Each Other Inside the Body to Target Tumors

June 22, 2011.

Tags: Nanoparticles, Nanomedicine, Nano-Oncology, Drug Delivery.



MIT researchers designed nanoparticles that can quickly locate a tumor, then set off a chemical reaction that attracts larger swarms of drug-delivering nanoparticles to the site. Scouting nanoparticles (blue) find tumor cells, then broadcast their location. Responding nanoparticles (red) swarm to the location carrying payloads of drugs, concentrating treatment where it is needed. Image: Gary Carlson

For decades, researchers have been working to develop nanoparticles that deliver cancer drugs directly to tumors, minimizing the toxic side effects of chemotherapy. However, even with the best of these nanoparticles, only about 1 percent of the drug typically reaches its intended target.

Now, a team of researchers from MIT Laboratory for Multiscale Regenerative Technologies, the Sanford-Burnham Medical Research Institute and the University of California at San Diego's Division of Physical Sciences have designed a new type of delivery system in which a first wave of nanoparticles homes in on the tumor, then calls in a much larger second wave that dispenses the cancer drug. **This communication between nanoparticles, enabled by the body's own biochemistry, boosted drug delivery to tumors by more than 40-fold in a mouse study.**

This new strategy could enhance the effectiveness of many drugs for cancer and other diseases, says Geoffrey von Maltzahn. "What we've demonstrated is that nanoparticles can be engineered to do things like communicate with each other in the body, and that these capabilities can improve the efficiency with which they find and treat diseases like cancer," von Maltzahn says.

Scientists **drew their inspiration from complex biological systems in which many components work together to achieve a common goal.** For example,

the immune system works through highly orchestrated cooperation between many different types of cells. "There are beautiful examples throughout biology where at a system scale, complex behaviors emerge as a result of interaction, cooperation and communication between simple individual components".

To pave the path for potential clinical trials and regulatory approval, the MIT researchers are now exploring ways to replace components of these cooperative nanosystems with drugs already being tested in patients. **Source: Working in harmony. MIT-designed nanoparticles communicate with each other inside the body to target tumors more efficiently** By Anne Trafton

Like swarming insects drawing crowds to a food source, a system of nanoparticles and engineered proteins can communicate with one another to raise the concentration of systemically administered drugs at the site of a tumor, a team of scientists has demonstrated.

The system harnesses one of the body's own communication pathways, one that coagulates blood, to accumulate drugs right where they are needed.

"We engineered a set of nanoparticles that trigger the body to grow blood clots around tumors. A second set of nanoparticles that recognizes the blood clots then delivers a dose of anti-cancer

drug to the tumor," said Michael Sailor, professor of chemistry and biochemistry at UC San Diego.

Source: Swarming Nanoparticles Communicate to Boost Drug Concentrations Near Tumors By Susan Brown

This work was detailed in the paper **"Nanoparticles that communicate in vivo to amplify tumour targeting"**

Abstract:

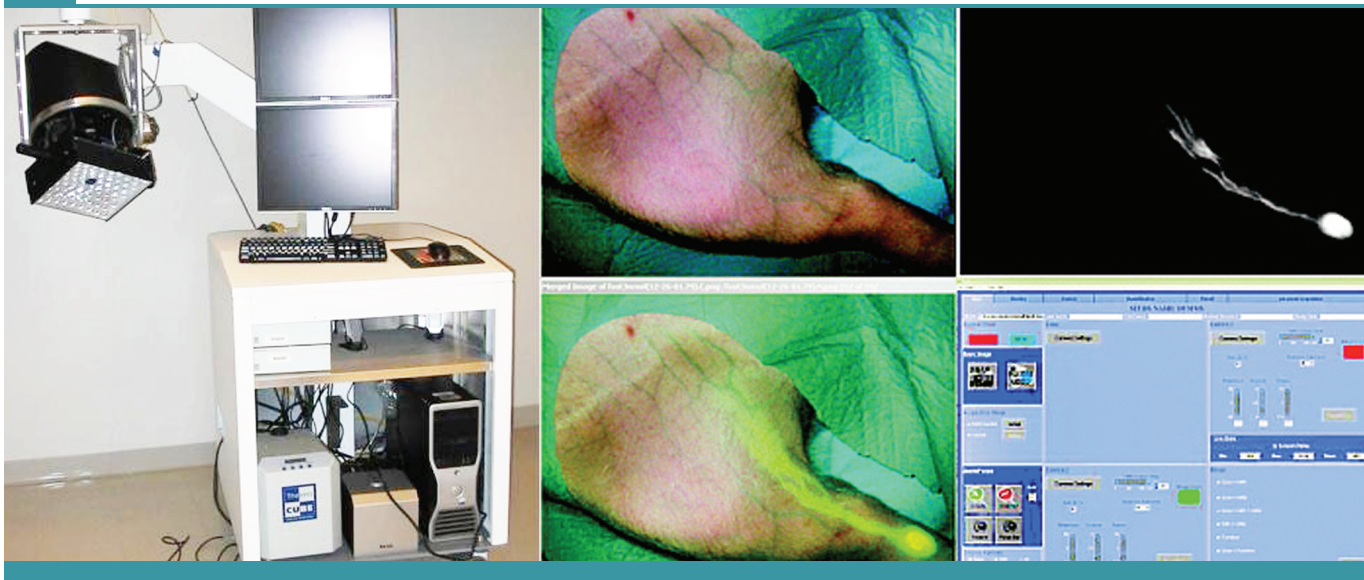
Geoffrey von Maltzahn, Ji-Ho Park, Kevin Y. Lin, Neetu Singh, Christian Schwöppe, Rolf Mesters, Wolfgang E. Berdel, Erkki Ruoslahti, Michael J. Sailor & Sangeeta N. Bhatia. 2011. **Nature Materials** doi:10.1038/nmat3049

Nanomedicines have enormous potential to improve the precision of cancer therapy, yet our ability to efficiently home these materials to regions of disease in vivo remains very limited. Inspired by the ability of communication to improve targeting in biological systems, such as inflammatory-cell recruitment to sites of disease, we construct systems where synthetic biological and nanotechnological components communicate to amplify disease targeting in vivo. These systems are composed of 'signalling' modules (nanoparticles or engineered proteins) that target tumours and then locally activate the coagulation cascade to broadcast tumour location to clot-targeted 'receiving' nanoparticles in circulation that carry a diagnostic or therapeutic cargo, thereby amplifying their delivery. We show that communicating nanoparticle systems can be composed of multiple types of signalling and receiving modules, can transmit information through multiple molecular pathways in coagulation, can operate autonomously and can target over 40 times higher doses of chemotherapeutics to tumours than non-communicating controls.

Scientists Chronicle Nanoparticles' Journey from the Lungs Into the Body

November 11, 2010.

Tags: Air, Nanoparticles, Nanotoxicology, Nano-Oncology, Images, Drug Delivery.



The Fluorescence-Assisted Resection and Exploration (FLARE) device. Credit: John V. Frangioni, M.D., Ph.D. Beth Israel Deaconess Medical Center, Boston. FLARE combines visible light (top left) and infrared (top right) into a single, perfectly registered image (bottom left) to show the path connecting a primary tumor with a neighboring lymph node (bright spot)

Using a novel, real-time imaging system, scientists have tracked a group of near-infrared fluorescent nanoparticles from the airspaces of the lungs, into the body and out again, providing a description of the characteristics and behavior of these minute particles which could be used in developing therapeutic agents to treat pulmonary disease, as well as offering a greater understanding of the health effects of air pollution.

The aim of this new study, led by investigators at Beth Israel Deaconess Medical Center (BIDMC) and the Harvard School of Public Health, was to determine the characteristics and parameters of inhaled nanoparticles that mediate their uptake into the body - from the external environment, across the alveolar lung surface and into the lymphatic system and blood stream and eventually to other organs. To do this, the scientists made use of the FLARE™ (Fluorescence-Assisted Resection and Exploration) imaging system, systematically varying the chemical composition, size, shape and surface charge of a group of near-infrared fluorescent nanoparticles to compare the

physiochemical properties of the various engineered particles. The investigators then tracked the movement of the varying nanoparticles in the lungs of rat models over a period of one hour, and also verified results using conventional radioactive tracers.

"The FLARE system enabled us to cut the number of experiments in half while performing direct comparisons of nanoparticles of different sizes, shapes and rigidities," explains Frangioni, whose laboratory developed the FLARE system for use in image-guided cancer surgery as well as other applications.

"This study complements our earlier work in which we defined the characteristics of nanoparticles that regulate efficient clearance from the body. With these new findings, which define the characteristics that regulate uptake into the body, **we've now described a complete 'cycle' of nanoparticle trafficking - from the environment, through the lungs, into the body, then out of the kidneys in urine and back to the environment,**" said Frangioni.

Source: Scientists Chronicle Nanoparticles' Journey From the Lungs Into the Body. This work is detailed in the paper "**Rapid translocation of nanoparticles from the lung airspaces to the body**" by Hak Soo Choi, Yoshitomo Ashitate, Jeong Heon Lee, Soon Hee Kim, Aya Matsui, Numpon Insin, Moungi G Bawendi, Manuela Semmler-Behnke, John V Frangioni & Akira Tsuda.

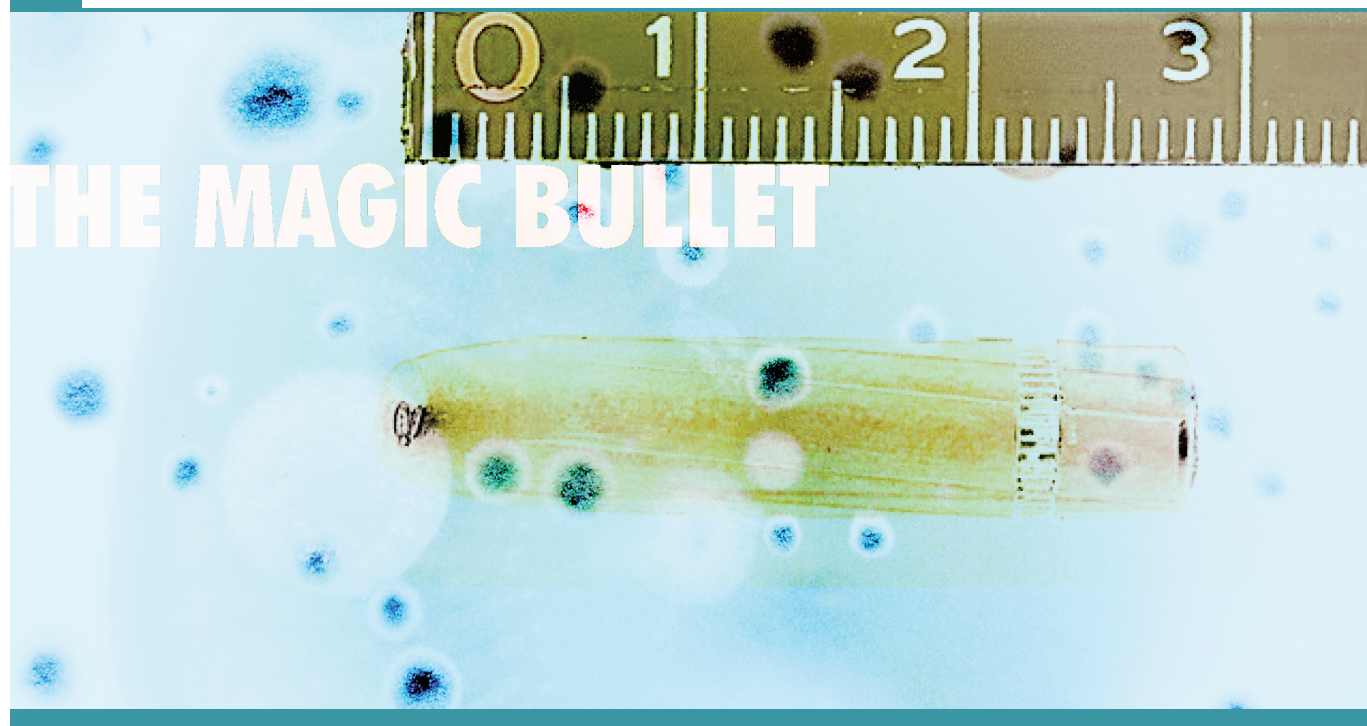
Abstract:

Nano-size particles show promise for pulmonary drug delivery, yet their behavior after deposition in the lung remains poorly understood. In this study, a series of near-infrared (NIR) fluorescent nanoparticles were systematically varied in chemical composition, shape, size and surface charge, and their biodistribution and elimination were quantified in rat models after lung instillation. We demonstrate that nanoparticles with hydrodynamic diameter (HD) less than ≈34 nm and a noncationic surface charge translocate rapidly from the lung to mediastinal lymph nodes. Nanoparticles of HD < 6 nm can traffic rapidly from the lungs to lymph nodes and the bloodstream, and then be subsequently cleared by the kidneys. We discuss the importance of these findings for drug delivery, air pollution and carcinogenesis.

Preferential Killing of Cancer Cells Using ZnO Nanoparticles

August 31, 2008.

Tags: Nanoparticles, Nanobiotechnology, Nano-Oncology.



Boise State researchers have made a remarkable breakthrough in cancer treatment that may provide the “magic bullet” for the debilitating effects of chemotherapy. The interdisciplinary group of researchers applied emerging nanotechnology techniques to traditional cancer research to come up with a highly effective method for the preferential killing of cancer cells while leaving ordinary cells healthy. This nanobiotechnology group is led by Boise State physics professor Alex Punnoose with strong contributions from biology professors Denise Wingett and Kevin Feris.

“One of the greatest challenges preventing advances in new therapeutic options for treating cancer is the inability of anticancer drugs to effectively differentiate between cancerous and normal healthy body cells,” said Wingett, a cancer researcher. “Many commonly used chemotherapeutic drugs target rapidly dividing cells but suffer from

a relatively low therapeutic index, which is the ratio of toxic dose to effective dose.” But the group discovered that **zinc-oxide nanoparticles can preferentially kill cancer cells without impacting normal cells**, a discovery that could potentially treat the cancer without the side effects caused by chemotherapy.

“Until now, no group in the world has been able to produce inherent selective cancer-killing ability in nanoparticles,” Wingett said. “Current chemotherapy drugs typically consist of single molecules and do not provide much room for manipulation of the molecule. But nanoparticles can be modified so that certain characteristics, like cancer-killing attributes, can be accentuated. Because of this, we think there is room for improvement in what we have already demonstrated.”

Wingett said the selectivity of these nanomaterials may be enhanced by

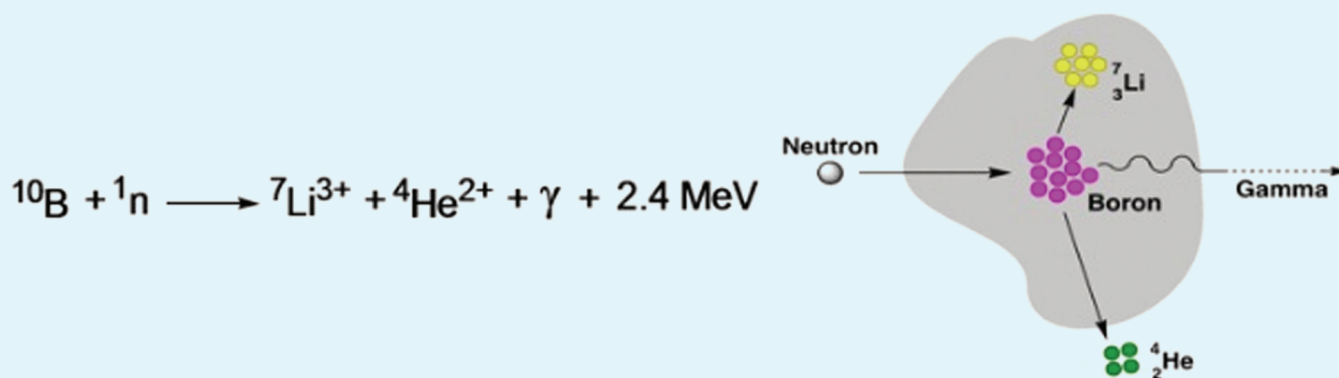
linking tumor-targeting proteins such as monoclonal antibodies, peptides, and small molecules to tumor-associated proteins, or by using nanoparticles for drug delivery. In addition to these future directions, the research team is exploring the possibility of altering the nanoparticles to further improve their inherent ability to kill cancer cells while sparing normal healthy body cells.

Source: Boise State Cancer Research Breakthrough May Be ‘Magic Bullet’ for Cancer Treatment. The group’s discovery is described in the paper “**Preferential Killing of Cancer Cells and Activated Human T Cells Using ZnO Nanoparticles**”, published in the journal *Nanotechnology*.

Breakthrough Cancer-Killing Treatment Has No Side-Effects

April 5, 2013.

Tags: Nano-Oncology, Nanomedicine.



Boron-Rich Nanoscale Delivery Agents for the Boron Neutron Capture Therapy of Cancer.
Credit: International Institute of Nano and Molecular Medicine

Cancer painfully ends more than 500,000 lives in the United States each year, according to the Centers for Disease Control and Prevention. The scientific crusade against cancer recently achieved a victory under the leadership of University of Missouri Curators' Professor M. Frederick Hawthorne. Hawthorne's team has developed **a new form of radiation therapy that successfully put cancer into remission in mice**. This innovative treatment produced none of the harmful side-effects of conventional chemo and radiation cancer therapies. Clinical trials in humans could begin soon after Hawthorne secures funding.

"Since the 1930s, scientists have sought success with a cancer treatment known as boron neutron capture therapy (BNCT)," said Hawthorne, a recent winner of the National Medal of Science awarded by President Obama in the White House. "Our team at MU's International Institute of Nano and Molecular Medicine finally found the way to make BNCT work by taking advantage of a cancer cell's biology with nanochemistry."

Cancer cells grow faster than normal cells

and in the process absorb more materials than normal cells. Hawthorne's team took advantage of that fact by getting cancer cells to take in and store a boron chemical designed by Hawthorne. **When those boron-infused cancer cells were exposed to neutrons, a subatomic particle, the boron atom shattered and selectively tore apart the cancer cells, sparing neighboring healthy cells.**

The physical properties of boron made Hawthorne's technique possible. A particular form of boron will split when it captures a neutron and release lithium, helium and energy. Like pool balls careening around a billiards table, the helium and lithium atoms penetrate the cancer cell and destroy it from the inside without harming the surrounding tissues.

"A wide variety of cancers can be attacked with our BNCT technique," Hawthorne said. "The technique worked excellently in mice. We are ready to move on to trials in larger animals, then people. However, before we can start treating humans, we will need to build suitable equipment and facilities. When it is built, MU will have the first radiation therapy of this kind in the world."

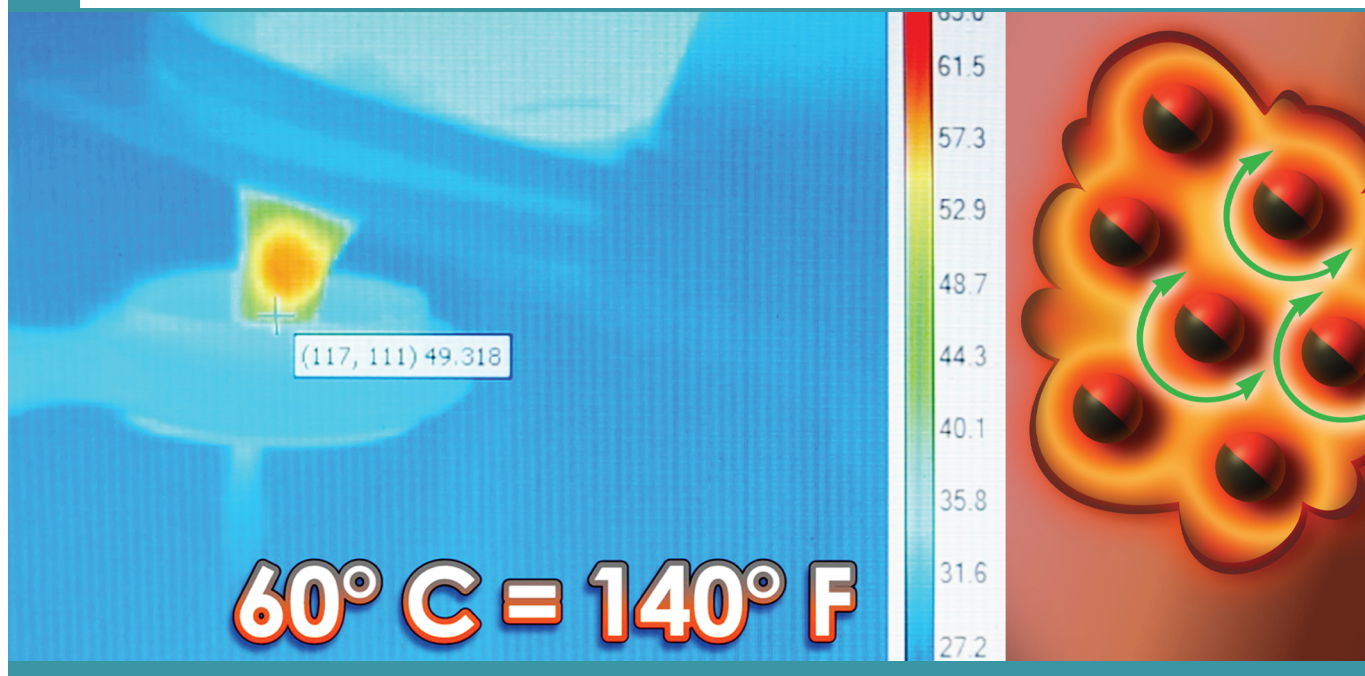
Hawthorne believes that his discovery was possible only at the University of Missouri because MU has three features that separate it from other universities in the nation, the reason Hawthorne came to MU from the University of California, Los Angeles in 2006.

"First, it is an example of a small number of universities in the United States with a large number of science and engineering disciplines on the same campus," said Hawthorne. "Second, the largest university research nuclear reactor is located at MU. Finally, it has strong, collegial biomedicine departments. This combination is unique." **Source: Breakthrough Cancer-Killing Treatment Has No Side-Effects, Says MU Researcher.** This work is detailed in the paper "**Boron neutron capture therapy demonstrated in mice bearing EMT6 tumors following selective delivery of boron by rationally designed liposomes**" by Peter J. Kueffer, Charles A. Maitz, Aslam A. Khan, Seth A. Schuster, Natalia I. Shlyakhina, Satish S. Jalisatgi, John D. Brockman, David W. Nigg, and M. Frederick Hawthorne.

Heated Nanoprobes to Destroy Breast Cancer Cells in Mice

July 15, 2007.

Tags: Nanomedicine, Nano-Oncology.



LEFT: An infrared camera shows iron particles heating a tumor to liquefaction, while adjacent healthy tissue stays cool and unharmed. RIGHT: Iron particles inside a tumor spin in an alternating magnetic field, generating enough heat to cook the cancer. Credits: Nanoprobes, Inc.

Next step will be testing in cancer patients

In experiments with laboratory mice that bear aggressive human breast cancers, UC Davis researchers have used hot nanoprobes to slow the growth of tumors - without damage to surrounding healthy tissue. "We have demonstrated that the system is feasible in laboratory mice. The next step will be clinical testing in patients" said Sally DeNardo, a professor of internal medicine and radiology at UC Davis and lead author of the study.

Many researchers have studied heat as a potential treatment for cancer, but the difficulty of confining heat within the tumor and predicting an effective heat dose has limited its use. The UC Davis research, carried out in collaboration with scientists from Triton BioSystems in Boston, seeks to solve this problem.

The experimental system uses bioprobes created by wedding magnetized iron-oxide

nanospheres to radiolabeled monoclonal antibodies. The bioprobes are cloaked in polymers and sugars that render them nearly invisible to the body's immune system.

"Using heat to kill cancer cells isn't a new concept," DeNardo said. "The biggest problems have been how to apply it to the tumor alone, how to predict the amount needed and how to determine its effectiveness. By combining nanotechnology, focused AMF therapy and quantitative molecular imaging techniques, we have developed a safer technique that could join other modalities as a treatment for breast and other cancers."

DeNardo, co-director of the Radiodiagnosis and Therapy Program at UC Davis, was the first investigator to use monoclonal antibodies in the delivery of radioimmunotherapy when she generated monoclonal antibodies against mouse melanoma in 1979. She was also the first

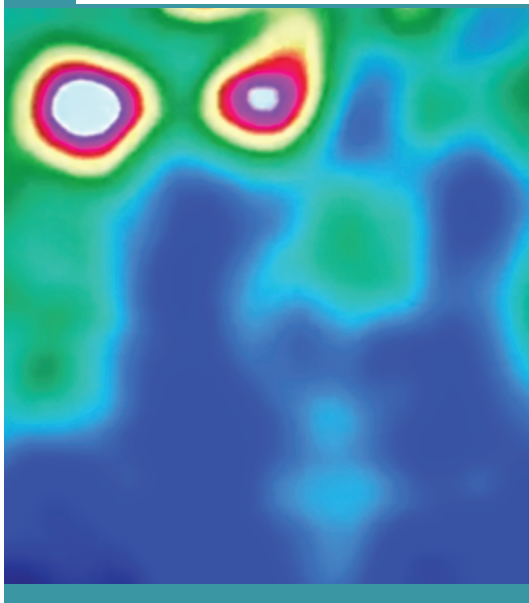
to demonstrate that radioimmunotherapy can be effective in the treatment of non-Hodgkin's B-cell lymphoma and chronic lymphocytic leukemia, and the first to describe the clinical use of radioimmunotherapy coupled with a biologically active antibody to treat breast cancer.

Source: UC Davis researchers use heated nanoprobes to destroy breast cancer cells in mice

Video Journey Into Nanotechnology

April 23, 2009.

Tags: Educational, Nano-Oncology, Video.



Frame from Video Journey Into Nanotechnology

In the fight against cancer, nanotechnology introduces **unique approaches to diagnosis and treatment** that could not even be imagined with conventional technology.

New tools engineered at sizes much smaller than a human cell will enable researchers and clinicians to detect cancer earlier, treat it with much greater precision and fewer side effects, and possibly stop the disease long before it can do any damage.

Imagine a nanoparticle that can be used to light up a tumor in an MRI, destroy cancer cells by converting magnetic fields into heat, and allow the physician to visually track the progress of treatment. To learn more about the possibilities of nanotechnology in cancer and explore the field, a Video Journey Into Nanotechnology. The National Cancer Institute (NCI), part of the National Institutes of Health, is engaged in efforts to harness the power of nanotechnology to radically change the way we diagnose, treat and prevent cancer. The NCI Alliance for Nanotechnology in Cancer is a comprehensive, systematized initiative encompassing the public and private sectors, designed to accelerate the application of the best capabilities of nanotechnology to cancer.

Source: [Video Journey Into Nanotechnology](#)

First Nanomedicine TV

February 1, 2011.

Tags: Nanomedicine, Video.



Frame from Animated Nanomedicine movie

Nanomed TV foresees to become the main hub for Nanomedicine thanks to its initiators, two major European players in nanomedicine: the European Technology Platform on Nanomedicine (ETPN) and Nanobiotix. Nanomed TV will make information accessible, aiming at answering what people need and wish to know about Nanomedicine.

This project is driven by Nanobiotix, a leading company in Nanomedicine focused on cancer treatment and the ETPN, an initiative led by the industry and set up together with the European Commission to address the application of nanotechnology to achieve breakthroughs in healthcare. NanomedTV is supported by renowned experts that bring together scientific, medical, regulatory, industrial and financial expertise.

According to Laurent Levy, co-founder and CEO of Nanobiotix, a 15 years long veteran in nanotechnologies : "People are looking for experts to advise them, not to ignore them. Thus, Nanomedicine experts need to inform in a trustful and comprehensive way on discoveries and new knowledge in order to speed up the adoption of Nanomedicine to the benefit of patients and the healthcare system."

Bertrand Loubaton, chairman of the ETPN, claims that "NanomedTV will contribute to the dissemination of novel medical approaches and will help to bring the interested communities - industry, academia, research bodies and public authorities as well as the individual patients - together and by that to create a transparent and reliable information channel."

Nanotechnologies represent a historical break that gives clinicians new tools in the fight against disease, trauma and other medical problems. Diagnoses can be made earlier and more quickly; medicines and other treatments can be better targeted and lead to fewer side effects. More importantly, nanomedicine can bring new options for treatment through new modes of action that are not based on biological interaction.

Nanomed TV will be reviewed by a group of experts before publishing. It will host qualified videos, podcasts, with medical, scientific, technical, industrial points of view. The content will show some shorts movies (from 1 to 15 minutes), podcasts, etc.

Source: [Launch of the NanomedTV](#)

Nano World Cancer Day: How Nanomedicine Contributes to Better Cancer Diagnostic and Therapy

February 1, 2013.

Tags: Nano-Oncology, Nanomedicine.



the key role of nanomedicine for cancer therapy, diagnoses and imaging.

In the framework of the World Cancer Day, the European Technology Platform of Nanomedicine (ETPN) and its partners will organize a European event on February the 1st on “How nanomedicine contributes to better cancer diagnostic and therapy”. Similar and simultaneous events will be organized in France and Portugal, **highlighting the importance of nanomedicine research for cancer on the European level.**

Radiotherapy, chemotherapy and surgery are part of the therapeutic arsenal for patients with cancer. New technologies associated with nanoparticles could provide more effective solutions to personalize diagnoses and treat these diseases, while improving targeted drug delivery and reducing side effects and collateral damages on the body. These breakthrough therapies based on nanomedicine are already a reality with concrete results, 60 nano-products on the market and more than 70 in the pipeline. Nanomedicine can go further in bringing new therapeutic mode of action into cells. For instance, nanoparticles can already be injected into the tumor and then be activated to produce a physical effect and destroy cancer cells locally.

In the press events across Europe, leading international stakeholders in the field will introduce examples highlighting the key role of nanomedicine for cancer therapy, diagnoses and imaging.

This year, these stakeholders across Europe who have already confirmed are:

National Cancer organizations:

Canceropole CLARA (FR)
Comprehensive Cancer Center (Charité University Hospital) (DE)
Instituto Português de Oncologia do Porto (PT)

SMEs: Nanobiotix (FR)

Universities / Public laboratories:

Thomas Jefferson University, Philadelphia (US), CNRS / Paris 11 University (FR), Ludwig-Maximilians University München (DE), Aachen University Hospital (DE), INL – International Iberian Nanotechnology Laboratory (Portugal-Spain), Universidad de Santiago de Compostela (Spain), University of Lisboa/ Faculty of Pharmacy (PT). Source: From Small tools for a big cause: How nanomedicine contributes to better cancer diagnostic and therapy.

Context:

April, 2012. First Targeted and Programmable Nanomedicine to Show Clinical Anti-Tumor Effects
November, 2011. A realistic look at the promises and perils of nanomedicine
July, 2011. First synthetic organ transplant
February, 2011. First Nanomedicine TV
Septembre, 2010. First scientific workshop on nanomedicines
July, 2010. World's first nanoparticle-based cancer treatment to come to market
May, 2009. Diagnosis through breath

Lessons Learned in Creating Biomedical Nanoparticles for Human Use

August 24, 2012.

Tags: Nanomedicine, Nano-Oncology, Nanomaterial.



Over the past six years, the National Cancer Institute's (NCI) Nanotechnology Characterization Laboratory (NCL), a key component of the NCI's Alliance for Nanotechnology in Cancer, **has characterized more than 250 different nanomaterials** developed by over 75 research groups. This extensive experience has given NCL staff a unique perspective on how to design safe and biocompatible nanomaterials for human use. In a paper the NCL team shared some of the lessons they have learned.

The NCL performs and standardizes the pre-clinical characterization of nanomaterials intended for cancer therapeutics and diagnostics developed by researchers from academia, government, and industry. The Lab serves as a national resource and knowledge base for cancer researchers, and facilitates the development and translation of nanoscale particles and devices for clinical applications. Scott McNeil, the NCL's director, and seven colleagues **compiled the common pitfalls that nonmaterial developers encounter on their path from basic research, to products that will be tested as agents for imaging or delivering drugs to tumors in humans.**

One important lesson for nanomaterial developers, who tend to be academic

researchers with little experience developing products intended for clinical use, is that they need to focus more on ensuring that the materials they develop for testing in animals, and eventually humans, are sterile. A recent review of 75 samples arriving at the NCL for testing found that more than one-third showed evidence of bacterial contamination.

Another important lesson was that commercially available materials, whether they are nanomaterials or chemicals used to make nanomaterials, are not always what they appear to be. In some cases, these raw materials are contaminated with bacterial toxins, in other cases the products do not meet the specifications advertised by the manufacturers. Dr. McNeil and his colleagues note that "it is in the researchers' best interest to always characterize materials before proceeding with synthesis and more expensive functionalization and biological testing."

NCL staff also found that investigators need to do a better job purifying their nanomaterials of residue remaining from the processes they use to manufacture their nanoparticles and other formulations. In some cases, nanomaterials that appeared to be toxic were in fact biocompatible. Instead, it was production impurities that

were causing toxicity issues. Additionally, NCL studies have shown that nanomaterial toxicity can often be eliminated by choosing slightly different starting materials that are incorporated into the final product but that do not play a role as an imaging agent or anticancer drug.

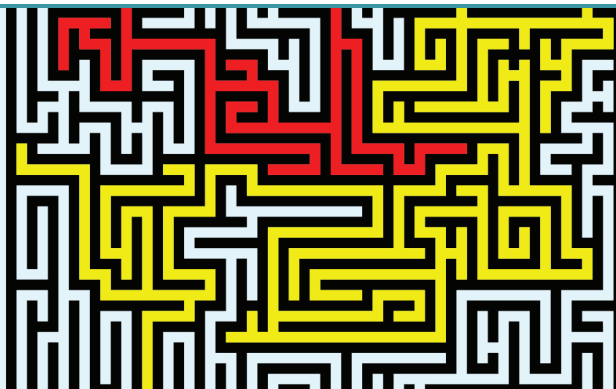
The last two lessons have to do with the importance of developing the right methods for assessing a nanomaterial's stability in the body and the rate at which it releases its cargo at the intended target, the tumor. NCL team leaders recommend that nanomaterial developers employ multiple assays before beginning animal studies to determine these characteristics of their nanomaterials because single assays can often paint an incomplete picture that can lead to wasted time and money.

Source: Lessons learned in creating biomedical nanoparticles for human use. This work is detailed in the paper "Common pitfalls in nanotechnology: lessons learned from NCI's Nanotechnology Characterization Laboratory" by Rachael M. Crist, Jennifer Hall Grossman, Anil K. Patri, Stephan T. Stern, Marina A. Dobrovolskaia, Pavan P. Adisheshaiah, Jeffrey D. Clogston and Scott E. McNeil.

Understanding How Cells Respond to Nanoparticles

November 24, 2010.

Tags: Nanoparticles, Nanotoxicology, Nano-Oncology, Drug Delivery.



Gold nanoparticles are showing real promise as vehicles for efficiently delivering therapeutic nucleic acids, such as disease-fighting genes and small interfering RNA (siRNA) molecules, to tumors. Now, a team of investigators from Northwestern University has shown that the safety of gold nanoparticle-nucleic acid formulations depends significantly on how the nucleic acids and nanoparticles are linked to one another, a finding with important implications for those researchers developing such constructs.

Chad Mirkin, co-principal investigator of the Northwestern University Center for Cancer Nanotechnology Excellence, one of nine such centers established by the National Cancer Institute (NCI), led the team of investigators that studied how cells respond to different nucleic acid-nanoparticle formulations.

To measure how cancer cells respond when they take up nanoparticles, Dr. Mirkin and his colleagues used a technique known as genome-wide expression profiling, which measures relative changes in global gene expression. The investigators added different types of nanoparticles to cancer cells growing in culture dishes and then obtained whole genome expression profiles for the cells. In all the experiments, the researchers attached non-targeting nucleic acids attached to the nanoparticles in order to minimize gene changes that might be triggered through a therapeutic effect

relating to a specific, designed interaction between the nucleic acid and a targeted gene.

The results of these comparison studies showed that **the surface properties of the nanoparticles had a profound impact on how a given nanoparticle impacts gene expression within a cell.** The researchers observed the most surprising and noteworthy difference when they compared two nanoparticles that differed only in the manner in which the nucleic acids were attached to the nanoparticle surface. Nanoparticles loosely linked to the nucleic acids triggered large-scale changes in gene expression, while in contrast, nanoparticles linked tightly to nucleic acids through a covalent chemical bond had virtually no effect on gene expression (See Comment by Matthew D. Massich below). These findings, the researchers noted, **show how important it is to fully characterize nanoparticles not only in terms of the shape and size, but also with respect to their surface properties.**

Source: Understanding How Cells Respond to Nanoparticles. Work supported in part by the National Cancer Institute (NCI) Alliance for Nanotechnology in Cancer, a comprehensive initiative designed to accelerate the application of nanotechnology to the prevention, diagnosis, and treatment of cancer. This work is detailed in the paper **"Cellular Response of Polyvalent**

Oligonucleotide-Gold Nanoparticle Conjugates" by Matthew D. Massich, David A. Giljohann, Abrin L. Schmucker, Pinal C. Patel, and Chad A. Mirkin.

Abstract:

Nanoparticles are finding utility in myriad biotechnological applications, including gene regulation, intracellular imaging, and medical diagnostics. Thus, evaluating the biocompatibility of these nanomaterials is imperative. Here we use genome-wide expression profiling to study the biological response of HeLa cells to gold nanoparticles functionalized with nucleic acids. Our study finds that the biological response to gold nanoparticles stabilized by weakly bound surface ligands is significant (cells recognize and react to the presence of the particles), yet when these same nanoparticles are stably functionalized with covalently attached nucleic acids, the cell shows no measurable response. This finding is important for researchers studying and using nanomaterials in biological settings, as it demonstrates how slight changes in surface chemistry and particle stability can lead to significant differences in cellular responses.

Comment by Matthew D. Massich
Dear Josep,

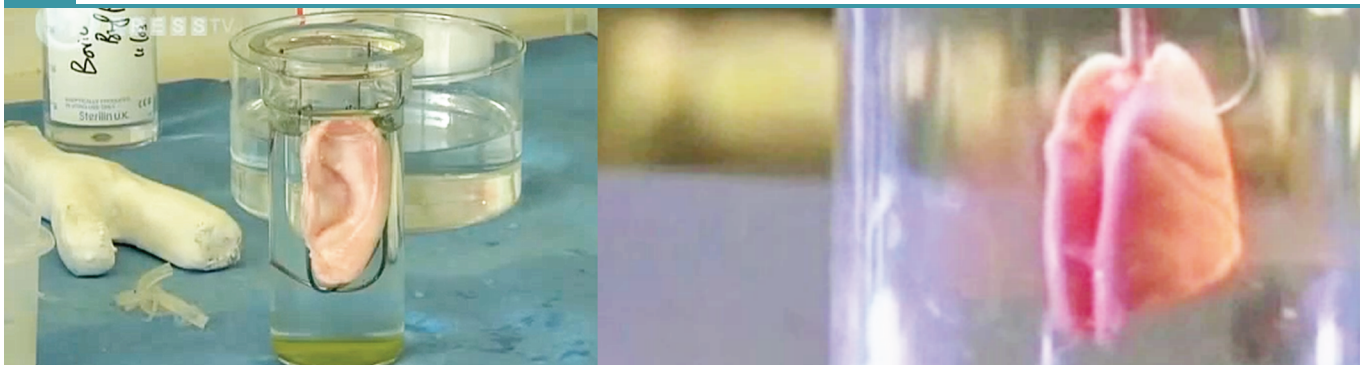
Thank you for featuring my recently published article on your website. I just wanted to make a point of clarification though. The nanoparticles that caused large-scale changes in gene expression were not functionalized with loosely bound nucleic acids, but rather they were stabilized by loosely (electrostatically) bound citrate molecules.

*Thank you,
Matt*

First Synthetic Organ Transplant

July 22, 2011.

Tags: Milestone, Nanomaterial, Nanomedicine, Nano-Oncology.



Frames from video in "Harvard Bioscience's Bioreactor Grows a Synthetic Tissue-Engineered Trachea Used in World's First Successful Human Transplantation"

For the first time in history, a patient has been given a new trachea made from a synthetic scaffold seeded with his own stem cells. The operation was performed at Karolinska University Hospital (Stockholm, Sweden), by professor Paolo Macchiarini and colleagues. Professor Macchiarini led an international team including professor Alexander Seifalian from the UCL (University College London, UK) who designed and built the nanocomposite tracheal scaffold and Harvard Bioscience (Boston, USA) who produced a specifically designed bioreactor used to seed the scaffold with the patient's own stem cells.

The successful transplantation of tissue engineered synthetic organs, referred to as regenerative medicine, could open new and very promising therapeutic possibilities for the thousands of patients who suffer from tracheal cancer or other conditions that destroy, block or constrict the airway. Professor Macchiarini has previously performed successful transplants of tissue engineered tracheas, but on those occasions the tracheas used were taken from organ donors and then reseeded with the patient's own stem cells. Transplantations of tissue engineered windpipes with synthetic scaffolds in combination with the patient's own stem cells as a standard procedure, means that patients will not have to wait for a suitable donor organ.

Source: First Successful Transplantation of a Synthetic Tissue Engineered Windpipe

Harvard Bioscience, a global developer, manufacturer and marketer of a broad range of tools to advance life science research and regenerative medicine, announces that its "InBreath" bioreactor was used for the world's first successful transplantation of a synthetic tissue engineered windpipe. For first time in history, a patient has been given a new trachea made from a synthetic scaffold seeded with his own stem cells in Harvard Bioscience's bioreactor. The patient, a 36-year old man who had been suffering from late stage tracheal cancer, that before this surgery would have been inoperable, is well on the way to a full recovery and was discharged from the hospital.

David Green, President of Harvard Bioscience, commented, "We congratulate Professor Macchiarini and the entire scientific and surgical team on achieving this landmark in the history of regenerative medicine."

Source: Harvard Bioscience's Bioreactor Grows a Synthetic Tissue-Engineered Trachea Used in World's First Successful Human Transplantation

The windpipe (trachea) implanted in this patient was developed using nanocomposite materials which were developed and patented by Alexander Seifalian, professor of nanotechnology and regenerative medicine at University College London, whose labs are based at the Royal Free Hospital. Together with Professor Paolo Macchiarini at Karolinska, who also holds an Honorary appointment at UCL, Professor

Seifalian designed and developed the trachea scaffold using a material known as a novel nanocomposite polymer.

Professor Seifalian has worked closely with UCL Business (UCLB), responsible for technology development and commercial transactions at UCL, to patent these materials and develop their use in medical devices. As well as being used for tissue scaffolds, the materials have other potential uses such as coronary stents and grafts.

A full size 'y-shaped' trachea scaffold was manufactured in Professor Seifalian's labs. This was accomplished using a Computerised Tomography scan of the patient as a guide, to create the exact shape and dimension needed. A mould was then made using glass.

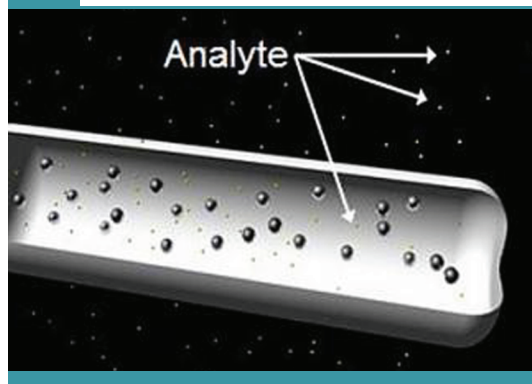
Professor Seifalian said: "What makes this procedure different is it's the first time that a wholly tissue engineered synthetic windpipe has been made and successfully transplanted, making it an important milestone for regenerative medicine. We expect there to be many more exciting applications for the novel polymers we have developed."

Source: UCL technology used in windpipe transplant

Nano-Implant Measures Tumor Growth, Treatment

February 26, 2007.

Tags: Nanomedicine, Nano-Oncology, Implant, Drug Delivery.



In this image, nanoparticles tailored to detect a particular molecule, or analyte, are suspended within a device that allows them to be delivered into a patient's body. Image courtesy: Cima research group.

A tiny implant now being developed at MIT could one day help doctors rapidly monitor the growth of tumors and the progress of chemotherapy in cancer patients. The implant contains nanoparticles that can be designed to test for different substances, including metabolites such as glucose and oxygen that are associated with tumor growth.

It can also track the effects of cancer drugs: Once inside a patient, the implant could reveal how much of a certain cancer drug has reached the tumor, helping doctors determine whether a treatment is working in a particular patient.

Such nanoparticles have been used before, but for the first time, the MIT researchers have encased the nanoparticles in a silicone delivery device, allowing them to remain in patients' bodies for an extended period of time. The device can be implanted directly into a tumor, allowing researchers to get a more direct look at what is happening in the tumor over time.

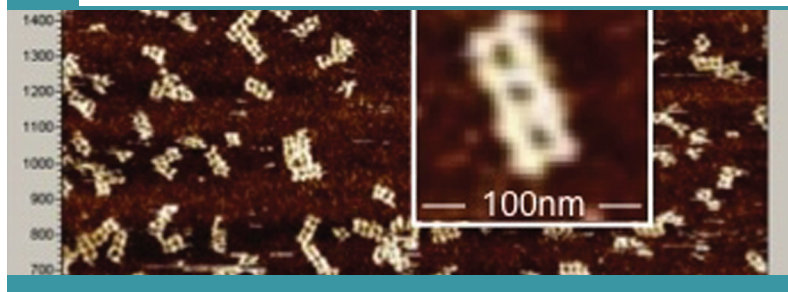
The new technique, known as implanted magnetic sensing, makes use of detection nanoparticles composed of iron oxide and coated with a sugar called dextran. Antibodies specific to the target molecules are attached to the surface of the particles. When the target molecules are present, they bind to the particles and cause them to clump together. That clumping can be detected by MRI (magnetic resonance imaging).

Source: **Nano-implant measures tumor growth, treatment**

Drag-and-Drop DNA

December 14, 2012.

Tags: Dna Nanotechnology, Self-Assembly, Nanoinformatics, Nano-Oncology.



A collection of pharmaceutical molecules is shown after self-assembly. The detail shows a single molecule, made up of strands of DNA, a therapeutic agent and other components that improve its ability to target cancer. Credit: Parabon NanoLabs.

Using a simple "drag-and-drop" computer interface and DNA self-assembly techniques, researchers have developed **a new approach for drug development** that could drastically reduce the time required to create and test medications.

In work supported by a National Science Foundation (NSF) Small Business Innovation Research grant, researchers from Parabon® NanoLabs of Reston, Va., recently developed and began evaluating a drug for combating the lethal brain cancer glioblastoma multiforme.

Now, with the support of an NSF Technology Enhancement for Commercial Partnerships (TECP) grant, Parabon has partnered with Janssen Research & Development, LLC, part of the Janssen Pharmaceutical Companies of Johnson & Johnson, to use the technology to create and test the efficacy of a new prostate cancer drug.

"We can now 'print,' molecule by molecule, exactly the compound that we want," says Steven Armentrout, the principal investigator on the NSF grants and co-developer of Parabon's technology. "What differentiates our nanotechnology from others is our ability to rapidly, and precisely, specify the placement of every atom in a compound that we design."

The new technology is called the Parabon Essemblix™ Drug Development Platform, and it combines their computer-aided design (CAD) software called inSçquo™ with nanoscale fabrication technology.

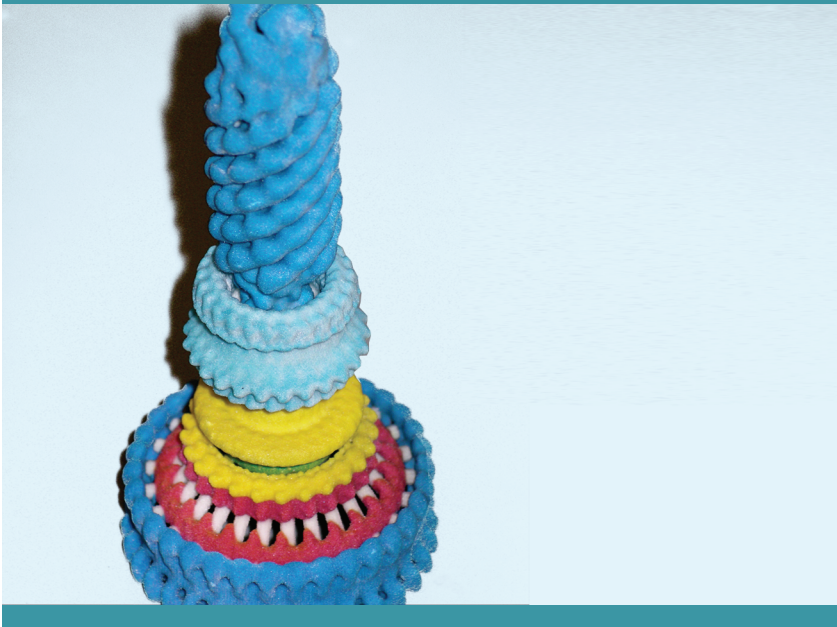
"Currently, most drugs are developed using a screening technique where you try a lot of candidate compounds against targets to 'see what sticks'," says Armentrout. "Instead, we're designing very specific drugs based on their molecular structure, with target molecules that bind to receptors on specific types of cancer cells. In plug-and-play fashion, we can swap in or swap out any of the functional components, as needed, for a range of treatment approaches."

Concurrently, Parabon is developing other applications for the technology, including synthetic vaccines for biodefense and gene therapies that can target disease, based on information from an individual's genome. The technology also has applications outside of medicine, and Parabon's co-founders Chris Dwyer and Michael Norton are building upon the initial NSF-supported work to develop processes to create nanoscale logic gates, devices critical for computing, and molecular nanosensors.

Source: **From Drag-and-Drop DNA.**

Flagellated Bacterial Nanorobots for Medical Interventions in the Human Body

October 31, 2008.



Bacterial flagellum. This is a physical model of a bacterial flagellum. It was imaged and modeled at Brandeis University in the DeRosier lab and printed at the University of Wisconsin - Madison. It was fabricated on a ZCorp Z406 printer from a VRML generated at Brandeis. Image: Alan Wolf (CC BY-SA 2.0).

“We show that a combination of various types of nanorobots will prove to be more important as we attend to enhance targeting in the smallest blood vessels found in the human microvasculature. As such, various interdependent concepts for the implementation of these different types of **medical bio-nanorobots** including nanorobots propelled in the microvasculature by flagellated bacteria to target deep regions in the human body are presented. Through experimental results and theoretical formulations, we also showed the advantages of integrating biological components and more specifically Magnetotactic Bacteria (MTB) for the development of hybrid (made of synthetic and biological components) nanorobots adapted to operate in the human microvasculature. We also show a method capable to track using MRI as imaging modality, steerable microbeads and MTB that could be integrated in the implementation of future sophisticated bionanorobots operating inside the complex vascular network. As such, we show that these nanorobots including the ones propelled by a single flagellated bacterium could be guided or controlled directly towards specific locations deep inside the human body. We also show experimentally that flagellated bacterial nanorobots could be propelled and steered in vivo through the interstitial region of a tumor for enhanced therapeutic results.”

Source: Flagellated Bacterial Nanorobots for Medical Interventions in the Human Body by Sylvain Martel, Ouajdi Felfoul, and Mahmood Mohammadi, École Polytechnique de Montréal. The researchers' latest work, was presented at the IEEE 2008 Biorobotics Conference, in the Symposium “Microrobotic Systems For Biomedical Applications”. See also World first in medical robotics and the video documental on their work, Sous-marin à résonance magnétique

Peer-Reviewed Papers

Label-Free Detection of Single Protein Using a Nanoplasmonic-Photonic Hybrid Microcavity

by Venkata R. Dantham¹, Stephen Holler^{1,2}, Curtis Barbre¹, David Keng¹, Vasily Kolchenko³, Stephen Arnold¹

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2 Department of Physics, Fordham University, Bronx, New York 10458, United States

3 Department of Biological Sciences, NYC College of Technology, Brooklyn, New York 11201, United States

Systemic Delivery of SapC-DOPS Has Antiangiogenic and Antitumor Effects Against Glioblastoma

by Jeffrey Wojton¹, Zhengtao Chu², Haritha Mathsyaraja^{3,4}, Walter H Meisen¹, Nicholas Denton¹, Chang-Hyuk Kwon^{1,4}, Lionel ML Chow⁵, Mary Palascak², Robert Franco², Tristan Bourdeau^{6,8}, Sherry Thornton⁶, Michael C Ostrowski^{3,4}, Balveen Kaur¹ and Xiaoyang Qi^{2,7}

1 Dardinger Laboratory for Neuro-oncology and Neurosciences, Department of Neurological Surgery, The Ohio State University Medical Center, Columbus, Ohio, USA

2 The Vontz Center for Molecular Studies, Division of Hematology/Oncology, Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA

3 Department of Molecular and Cellular Biochemistry, The Ohio State University Medical Center, Columbus, Ohio, USA

4 Solid Tumor Program at the James Comprehensive Cancer Center, The Ohio State University Medical Center, Columbus, Ohio, USA

5 Division of Oncology, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA

6 Division of Rheumatology, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA

7 Human Genetics, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA

8 Current address: Nestle Research Center, Lausanne, Switzerland

“pH phoresis”: A new concept that can be used for improving drug delivery to tumor cells

by You-Yeon Wona^{1,2,3}, Hoyoung Lee¹

1 School of Chemical Engineering, Purdue University, West Lafayette, IN 47907, USA

2 Bindley Bioscience Center, Purdue University, West Lafayette, IN 47907, USA

3 Center for Theragnosis, Biomedical Research Institute, Korea Institute of Science and Technology (KIST), Seoul 136-791, Republic of Korea

Nanoscale Obstacle Arrays Frustrate Transport of EphA2–Ephrin-A1 Clusters in Cancer Cell Lines

by Theobald Lohmüller^{1,3}, Qian Xu^{2,3}, and Jay T. Groves^{1,2,3}

1 Department of Chemistry and

2 Biophysics Graduate Group, Howard Hughes Medical Institute, University of California, Berkeley, California 94720, United States

3 The Physical Biosciences and Materials Sciences Divisions, Lawrence Berkeley National Laboratory, Berkeley, California 94720, United States

Self-assembled, aptamer-tethered DNA nanotrains for targeted transport of molecular drugs in cancer theranostics

by Guizhi Zhu^{1,2,3}, Jing Zheng^{1,2}, Erqun Song^{2,4}, Michael Donovan¹, Kejing Zhang², Chen Liu⁵, Weihong Tan^{1,2,3}

1 Molecular Science and Biomedicine Laboratory, State Key Laboratory of Chemo/Bio-Sensing and Chemometrics, College of Biology and College of Chemistry and Chemical Engineering, Collaborative Innovation Center for Chemistry and Molecular Medicine, Hunan University, Changsha 410082, China;

2 Department of Chemistry, Center for Research at Bio/Nano Interface, Shands Cancer Center, University of Florida Genetics Institute and McKnight Brain Institute, University of Florida, Gainesville, FL 32611-7200;

3 Department of Physiology and Functional Genomics, University of Florida, Gainesville, FL 32611;

4 Key Laboratory of Luminescence and Real-Time Analysis of the Ministry of Education, College of Pharmaceutical Sciences, Southwest University, Chongqing 400715, China; and

5 Department of Pathology and Laboratory Medicine, Shands Cancer Center, University of Florida, Gainesville, FL 32611

Boron neutron capture therapy demonstrated in mice bearing EMT6 tumors following selective delivery of boron

by rationally designed liposomes by Peter J. Kueffer, Charles A. Maitz, Aslam A. Khan, Seth A. Schuster, Natalia I. Shlyakhtina, Satish S. Jalisatgi, John D. Brockman, David W. Nigg, M. Frederick Hawthorne

International Institute of Nano and Molecular Medicine, University of Missouri, Columbia, MO 65211

First-in-Man Trial of an RNA Interference Therapeutic Targeting VEGF and KSP in Cancer Patients with Liver Involvement

by Josep Tabernero¹, Geoffrey I. Shapiro², Patricia M. LoRusso³, Andres Cervantes⁴, Gary K. Schwartz⁵, Glen J. Weiss⁶, Luis Paz-Ares⁷, Daniel C. Cho⁸, Jeffrey R. Infante⁹, Maria Alsina¹, Mrinal M. Gounder¹⁰, Rick Falzone¹¹, Jamie Harrop¹¹, Amy C. Seila White¹², Iva Toudjarska¹², David Bumcrot¹², Rachel E. Meyers¹², Gregory Hinkle¹², Nenad Svrzikapa¹², Renta M. Hutabarat¹¹, Valerie A. Clausen¹¹, Jeff Cehelsky¹¹, Saraswathy V. Nochur¹³, Christina Gamba-Vitalo¹³, Akshay K. Vaishnav¹⁴, Dinah W.Y. Sah¹⁵, Jared A. Gollob¹⁶, Howard A. Burris III¹⁷

1 Medical Oncology, Vall d'Hebron University Hospital

2 Medical Oncology, Dana-Farber Cancer Institute

3 Oncology, Karmanos Cancer Institute

4 Department of Hematology and Medical Oncology, University Hospital Valencia

5 Laboratory of New Drug Development, Department of Medicine, Memorial Sloan-Kettering Cancer Center

6 Cancer and Cell Biology, TGen

7 Medical Oncology, Hospital Universitario Virgen del Rocío

8 Hematology and Oncology, Beth Israel Deaconess Medical Center

9 Drug Development Unit, SCRI/Tennessee Oncology, PLLC

10 Medicine, Memorial Sloan-Kettering Cancer Center

11 Clinical, Alnylam Pharmaceuticals

12 Research, Alnylam Pharmaceuticals

13 Development, Alnylam Pharmaceuticals, Inc.

14

15 Research, Alnylam Pharmaceuticals Inc

16 Clinical Development, Alnylam Pharmaceuticals

17 Sarah Cannon Research Institute, Sarah Cannon Research Institute

Synthetic nanoparticles functionalized with biomimetic leukocyte membranes possess cell-like functions

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The nanomechanical signature of breast cancer

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Common pitfalls in nanotechnology: lessons learned from NCI's Nanotechnology Characterization Laboratory

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Three-dimensional orientation-unlimited polarization encryption by a single optically configured vectorial beam by Xiangping Li¹, Tzu-Hsiang Lan^{1,2}, Chung-Hao Tien², Min Gu¹

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Preclinical Development and Clinical Translation of a PSMA-Targeted Docetaxel Nanoparticle with a Differentiated Pharmacological Profile

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Nanoparticles that communicate in vivo to amplify tumour targeting

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Cellular Response of Polyvalent Oligonucleotide-Gold Nanoparticle Conjugates

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Rapid translocation of nanoparticles from the lung airspaces to the body

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In vivo nano-imaging of membrane dynamics in metastatic tumor cells using quantum dots

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Label-free biomarker detection from whole blood

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Sniffing the Unique “Odor Print” of Non-Small-Cell Lung Cancer with Gold Nanoparticles

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Diagnosing lung cancer in exhaled breath using gold nanoparticles

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An electronic nose in the discrimination of patients with non-small cell lung cancer and COPD

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Sniffing Chronic Renal Failure in Rat Model by an Array of Random Networks of Single-Walled Carbon Nanotubes

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Partial-wave microscopic spectroscopy detects subwavelength refractive index fluctuations: an application to cancer diagnosis

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Targeted delivery of cisplatin to prostate cancer cells by aptamer functionalized Pt(IV) prodrug-PLGA-PEG nanoparticles

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Enhancement of In Vivo Anticancer Effects of Cisplatin by Incorporation Inside Single-Wall Carbon Nanohorns

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Nanoparticle therapeutics: an emerging treatment modality for cancer

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Preferential killing of cancer cells and activated human T cells using ZnO nanoparticles

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Cancer cells assemble and align gold nanorods conjugated to antibodies to produce highly enhanced, sharp, and polarized surface Raman spectra: a potential cancer diagnostic marker

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Gold Nanorods Coated with Multilayer Polyelectrolyte as Contrast Agents for Multimodal Imaging

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Soluble Single-Walled Carbon Nanotubes as Longboat Delivery Systems for Platinum(IV) Anticancer Drug Design
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Targeting of cancer cells with ferrimagnetic ferritin cage nanoparticles

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Epilogue

Where are teletransportation and the flying cars? Drones and Skipe?

Regarding the promises made by scientists about the potential of nanomedicine during the last decade, one could argue that very few have been delivered yet. Recently an editorial in Drug Delivery Reviews questioned if the wave was already cresting for nanomedicine [1], already! It may happen that at the end only few sequels will remain and the real benefits of nanotechnology applied to medicine will be welcome but scarce.

I am not sure about that, first we may be neglecting parts of the real impact of all the effort in nanomedicine, as in improved hemodialysis membranes (with nanometric pores) or implant surface modifications (nanostructured). Second, it is true that one could say that the potential of nanomedicine is still in the platonic phase, however, if we do not focus only on what do we have but on how does it behave, it is easy to understand why we are advancing so slowly. It is too big for us to get it working quickly, as Gmail or Facebook. There are very few companies able to produce GMP nanoparticles as there are very few CROs trained to work with them, as there is poor knowledge on its characterization and nanotechnology does not fit in the framework of regulation. Additionally, we have conceptual shortages to control and design it. We are not as smart as we wish. We suffer an excess of productivity forces, we produce a number of experiments that go onto papers and conferences which are wrongly planned and wrongly interpreted: Unstable nanoparticles designed as drug delivery vehicles aggregate and rain on top of the *in vitro* cell model increasing dose and outperforming controls, as much as they aggregate at the point of injection delivering nothing.

[1] R. Juliano. Nanomedicine, is the wave cresting? Nature Reviews Drug Discovery 2013, 12, 171-172
<http://www.nature.com/nrd/journal/v12/n3/full/nrd3958.html>

Yet, both the modularity and tunability of nanoparticles properties which are inserted into the biochemical machinery has a tremendous potential to revolutionize the whole field of medicine. Nanoparticles have the ability to monitor and manipulate biological states as much as assist to virtually all the existing forms of medicine, contributing in diagnostic, monitoring and therapy. Nanomedicine is a tool that interferes with unique and high precision with the biological systems, but that we do not control properly yet. In the immediate future nanoparticles may have a significant impact in multimodal therapy and personalized therapy. Nanoparticles are ideal scaffolds to hold different drugs and they may also serve as contrasts agents, radio enhancers and hyperthermia agents all in one. This is the modular aspect of nanomedicine. Besides, as we advance in personalizing medicine, the ability to tune the kinetic and dynamic properties of the active principle using nanoparticles is high. For example, Resovist or Cisplatin conjugated to a gold nanoparticle can be prescribed in cases of renal deficiencies, or angiographies to detect permeability of the target tumor or organ before treatment or it may reveal early symptoms of permeability alteration, precluding disease.

As we are still in a development phase in front of a vast complexity, it is clear that the better possible investment is in education and training. And we learn by doing. And wisdom comes from experience which comes from error. The way may be as long as the future bright.



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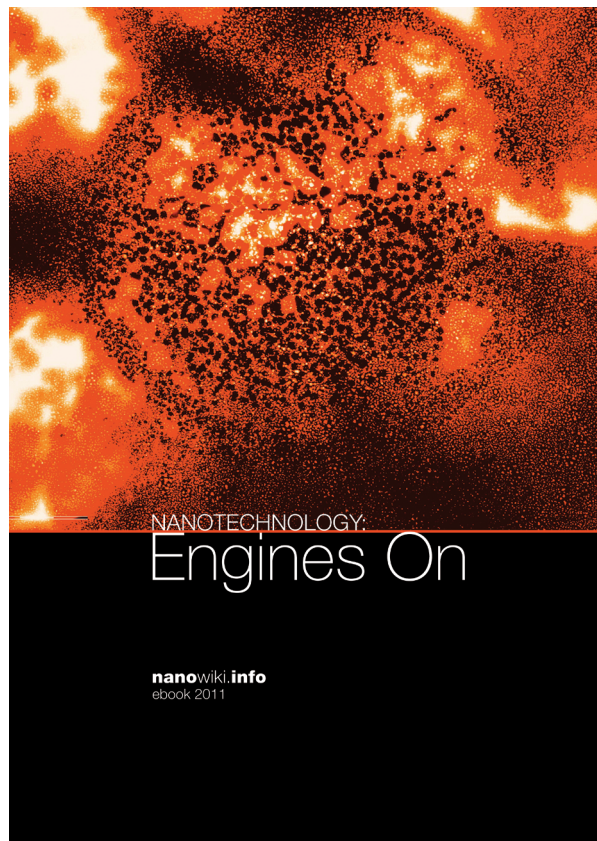
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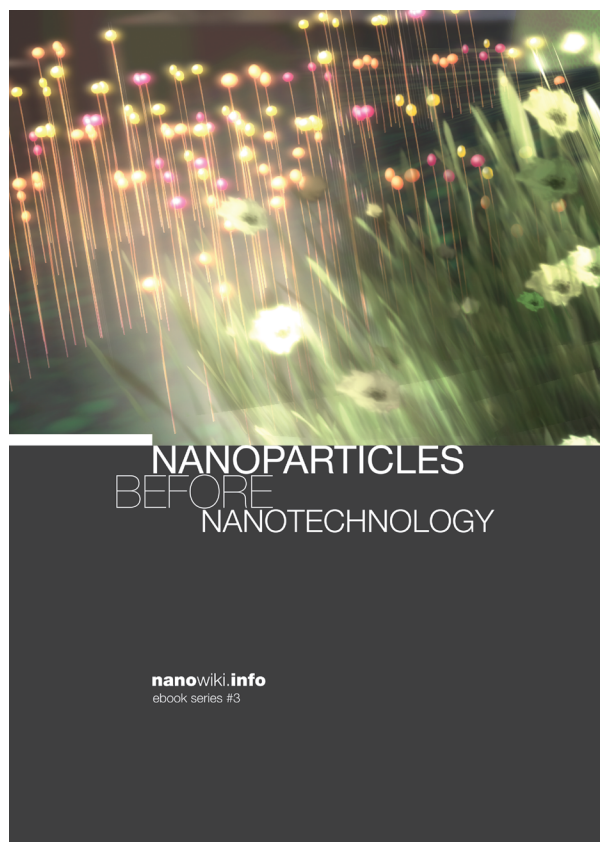
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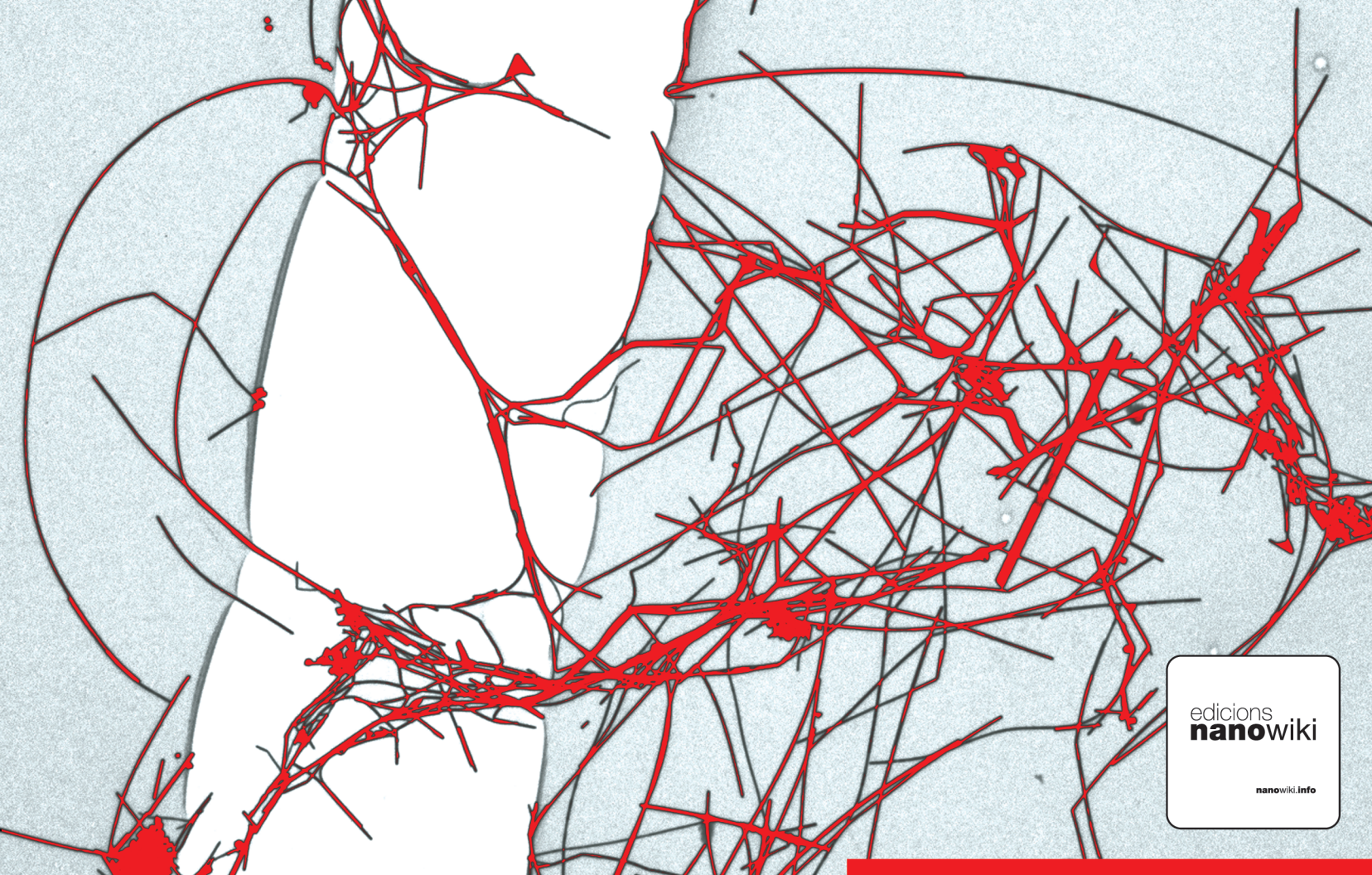
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*“Far from the public perception
that nanotechnology and nanomedicine
are still trending topics of science fiction”*

Simo Schwartz,
Director Cibbim-Nanomedicine,
Vall d'Hebron Institut de Recerca (VHIR)

- **An Introduction to the Nano-Oncology**, the Most Promising and Recent Contribution to Fight Cancer
- **The State-of-the-Art of this New Paradigm**, the Cancer Nanomedicine

Cancer is a leading cause of disease-related mortality, and with the increasing lifespan, it is predicted to be the cause of 50% of deaths in the 1st world population. Despite huge efforts, medical science has been unable to generate a “magic anticancer drug”, that is, a drug that can cure cancer completely and efficiently. The reason for this is that fundamental problems lie not in the drug itself, but in the way in which it is delivered and how it reaches the tumour. This lack of control and precision is present in other therapies, where a lack of specificity can thus damage healthy cells. One of the major goals in nanomedicine is to apply nanotechnology for the sustained, controlled and targeted delivery of therapeutic agents and radiosensitisers.

ABOUT THE AUTHORS:

Pr. Víctor Puentes has an ICREA research Profesorship on inorganic Nanoparticles. He has a degree on chemistry and chemical engineering and a PhD on physics, and he is currently working on the study of the energy and mass transfer between small aggregates of inorganic atoms and their environment, sharing his time between the Catalan Institute of Nanotechnology (ICN2) and the Research Institute of the Vall d'Hebró University Hospital (VHIR) .

Josep Saldaña is a tracker and contextualizer —Nanotechnology since 2005 for NanoWiki, and Biogas since 2014 for Applied Nanoparticles. Co-author of the NanoWiki book series. Passionate of the nanosatellites, a paradigm shift in the space exploration through the use of the nanotechnology.

Joan Escofet is a content designer. With an education on art and architecture, since 1996 he works on the construction of the visual image to convey meaning for grassroots urban participatory projects, nanotechnology books, and other collaborative projects to reveal context.



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